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Original Communications

THE INTRAVENOUS ADMINISTRATION OF SMALL DOSES OF CASEIN HYDROLYSATE TO NEPHROTIC CHILDREN AND ITS EFFECT UPON THE NITROGEN BALANCE AND PLASMA AMINO ACID LEVEL

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RECENTLY Farr and MacFadyen[1] reported finding a chronic plasma hypoaminoacidemia in nephrotic children and an acute exacerbation of this plasma amino acid deficit during nephrotic crises. Failure to control the plasma amino acid deficit on diets which promote optimal nitrogen assimilation in nephrotic children[2] led to the consideration of the therapeutic use of amino acid mixtures. Van Slyke and Meyer[3] showed that moderate amounts of amino acids given to dogs intravenously were removed rapidly from the blood stream and there were no apparent toxic effects. Because of the difficulties of preparing a satisfactory digest for human use, there was little further work reported on this problem until recently. In 1937, Elman[4] reported studies showing the practicability of casein digests as a source of nutritional nitrogen. Elman gave the digest intravenously and reported no severe reactions. Farr and MacFadyen[5] have reported further studies on nephrotic children which show that amino acids given intravenously are not immediately lost in the urine. This demonstrated the feasibility of this procedure for providing an extra source of amino acids in these patients. The present study was carried out to determine the effects upon the level of the plasma amino acids and upon the nitrogen balance of intravenous administration of a casein digest to children with the nephrotic syndrome.

MATERIALS AND METHODS

The nitrogen content of the diets was calculated from standard tables on food analysis. Throughout the period of study the same weekly diet

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was used. This permitted some variation in the daily menu and provided for a check on any inaccuracies of the calculated diet since the patients received the same foodstuffs during periods of amino acid administration and rest periods.

The urine samples were collected in clean sterile bottles, and whenever practicable, the patient voided directly into the bottle. No preservative was used. At the end of each twelve-hour period, each bottle was tightly stoppered and stored in the icebox until the end of the metabolic interval of study. At this time the entire urine specimen was thoroughly mixed, and aliquots were removed for analysis. Stool specimens were collected in clean pots, sent to the laboratory immediately after they were obtained, and transferred quantitatively to a concentrated sulfuric acid mixture. At the end of each period, the acid stool mixture was thoroughly mixed, made up to a convenient volume, and aliquots were removed for analysis. The beginning of each period was marked by feeding the patients 0.2 Gm. of carmine with breakfast, and the first stool containing carmine was taken as the first specimen of the ensuing period. No laxatives were necessary at any time.

Standard macro-Kjeldahl procedures were used for determining total stool nitrogen and urine nonprotein nitrogen after deproteinization with trichloracetic acid. Urine protein nitrogen was determined by a slight modification of the biuret colorimetric procedure of Hiller.[6] Urea plus ammonia nitrogen in the urine was determined by the method of Van Slyke and Kugel.[7] Plasma amino acid nitrogen was determined by the ninhydrin-CO_2 method of MacFadyen and Van Slyke.[8] The other clinical chemical analyses were carried out by the methods routinely used in this laboratory.[9-14]

The casein digest* used was an enzymatic product, required no additional amino acids, and satisfied the nutritional needs of rats.[15] The dry powder, packed in vacuum sealed cans, was kept unopened in the icebox until needed. The dry powder was weighed and dissolved in hot fresh triple distilled water at about 100° C. At this temperature solution was readily effected. Enough powder was used to give a solution containing approximately 10 per cent casein hydrolysate by weight and to yield lots of about 5 liters of the final solution. After solution was apparently complete, the material was kept on the steam bath for from thirty minutes to one hour, filtered through a Seitz filter while hot, bottled aseptically in lots of 100 c.c., autoclaved and stored in the icebox until used. The final solution had a reddish chestnut-brown color. The pH of the final product determined with a glass electrode averaged 4.45. No buffers were added. Material prepared in this way has been used after six months in the icebox with no reactions in the patient following its use. In some bottles a flocculent black precipitate formed after a few

*Obtained through the generosity of Mead Johnson and Company.

days in the icebox. This was removed before use by filtering through a sterile gauze square. Prior to clinical use, an aliquot of each lot was tested in rabbits for chill-producing substance.* If this test was satisfactory, the solution was ready for clinical trial.

CLINICAL COURSE OF PATIENTS DURING STUDY AND EXPERIMENTAL PROCEDURES

Four patients on the wards of the hospital were selected for study, two males, J. C., aged 6 years, and W. O'B., aged 4 years, and two females, R. Q., aged 7 years, and E. S., aged 7 years. All had been under observation on the hospital wards for several months prior to beginning this study. All had a history of insidious onset of edema without antecedent infection. At the time this study was begun, all had characteristically low plasma proteins, normal hemoglobin, normal blood urea nitrogen, normal blood pressure, normal urea clearance, and absence of hematuria. They were free from obvious acute or focal infection and had no clinically demonstrable edema or ascites. Previously, for three months, nitrogen balance studies had been carried out on three of the patients who had been on weighed calculated diets of approximately the same content as used in this study. One patient, E. S., had been on an approximate unweighed diet of the same proportions until two weeks prior to beginning this study, when she was started on the weighed and calculated diet used in these observations. Laboratory and clinical findings on these patients are summarized in Figs. 1 to 4. The present study was carried out on J. C. during months twenty-five to twenty-nine, on W. O'B. during months five to nine, on R. Q. during months six to nine, on E. S. during months fifty to fifty-four.

The four children were observed on a nitrogen balance study for fifteen consecutive weeks. A résumé of the diets used during the period of observation is given in Table I. Two one-week periods of study were completed before any amino acids were given intravenously. During the third period, 10 per cent casein hydrolysate solution mixed with an equal volume of 10 per cent glucose was given before breakfast on the first, third, and fifth days. The solution was allowed to run into the vein by gravity. A 20 gauge needle was used, and the bottom of the infusion flask was about 20 inches above the vein. At the conclusion of each amino acid infusion, a few cubic centimeters of 5 or 10 per cent glucose were run in to insure complete administration of the digest. The same technique of administration was used during all subsequent periods. No amino acids or glucose were given on the second, fourth, sixth, and seventh days. The quantity given to each patient varied, since the infusion was discontinued promptly when the patient became nauseated. W. O'B. was given 10, 2.7, and 5 Gm. of the amino acids; J. C. was given 5, 2, and 5 Gm.; R. Q. was given 10, 2.5, and 5 Gm.;

*I am indebted to Dr. Kenneth Goodner who carried out these tests in his laboratory.

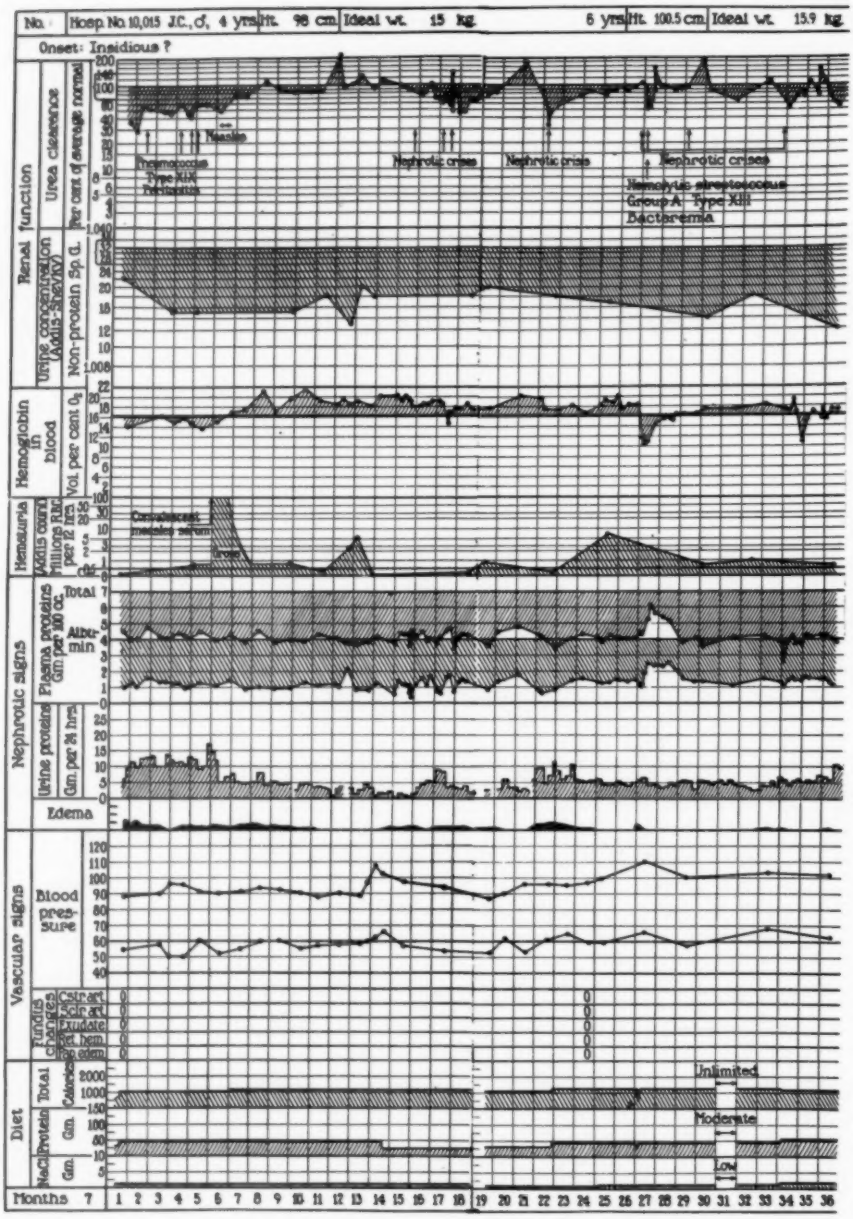

Fig. 1.—Graphic summary of course of J. C. since admission to the hospital. The present study covers months twenty-five through twenty-eight. Note the absence of effect upon renal function following the hemolytic streptococcus infection in month twenty-seven.

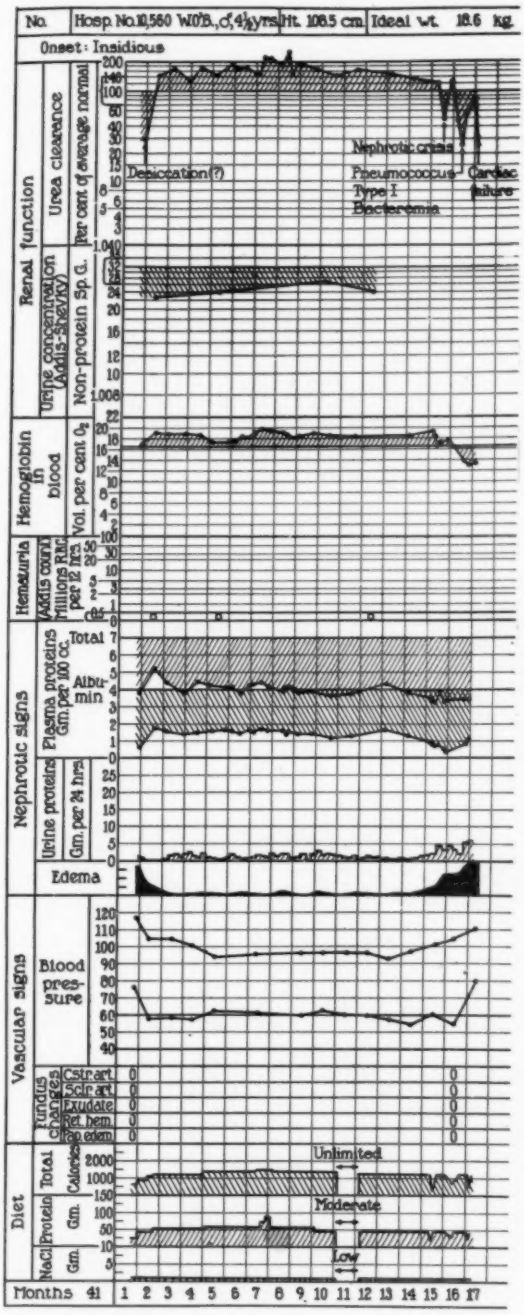

Fig. 2.—Graphic summary of course of W. O'B. since admission to the hospital. The present study covers months five to eight.

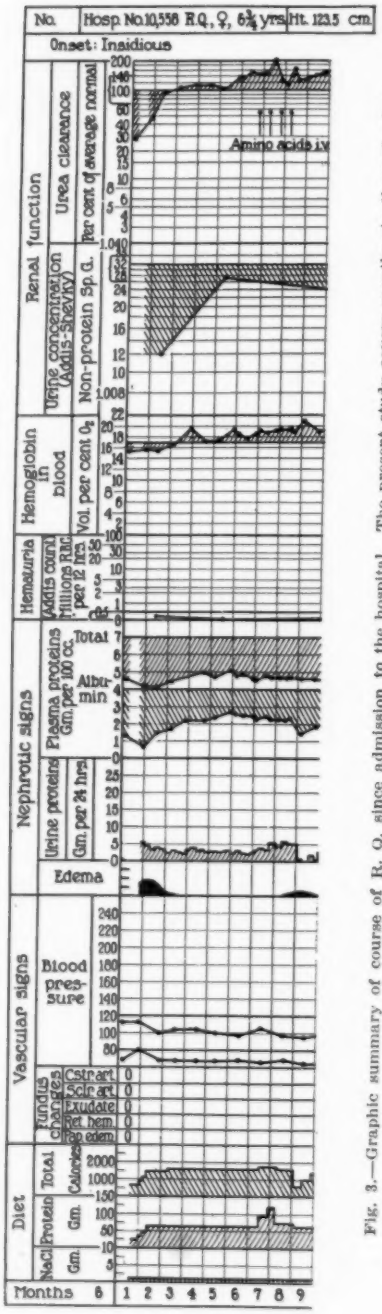

Fig. 3.—Graphic summary of course of R. Q. since admission to the hospital. The present study covers months six through nine.

E. S. was given 5, 2.6, and 5 Gm. A second control study of three one-week periods followed. During the seventh period, 5 Gm. of casein hydrolysate in the 10 per cent solution were given each morning before breakfast for five successive days to each of the four patients. Glucose was not administered simultaneously during this

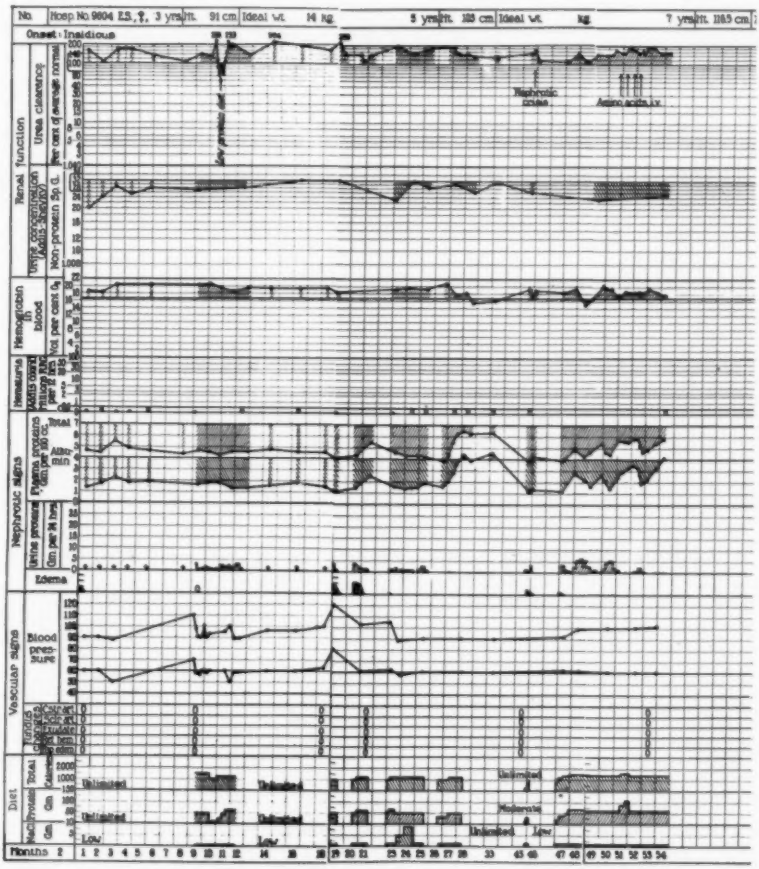

Fig. 4.—Graphic summary of course of E. S. since admission to the hospital. The present study covers months fifty through fifty-three. This child made a complete recovery from her first attack in the twenty-eighth month and was well until three weeks before readmission in the forty-fifth month. She has made a complete recovery from her second attack and now has been well for ten months.

period. The first day of the seventh period J. C. developed a fever of 101° F. which returned to normal in three hours after amino acids had been given. He complained of a scratchy throat. Physical examination was negative, except for a slight reddening of the throat. He had no more fever during this period. The first day of the eighth

TABLE I

SUMMARY OF DIETS FED DURING BALANCE EXPERIMENT SHOWING AMOUNTS OF PROTEIN, FAT, AND CARBOHYDRATE FED DAILY DURING EACH PERIOD

PATIENT	IDEAL WEIGHT (KG.)	ACTUAL WEIGHT (KG.)	PERIODS	AVERAGE DAILY FOOD INTAKE								PERCENTAGE OF CALORIES FROM		
				PROTEIN (GM.)	FAT (GM.)	CARBOHYDRATE (GM.)	CALORIES	PROTEIN (GM./KG.)	FAT (GM./KG.)	CARBOHYDRATE (GM./KG.)	CALORIES (PER KG.)	PROTEIN	FAT	CARBOHYDRATE
J. C.*	17.2	18.0	1-16	45	45	171	1,270	2.6	2.6	9.9	74	14	32	54
R. Q.	24.4	21.2	1-7	67	67	196	1,650	2.8	2.8	8.0	68	19	42	47
			8-9	98	67	194	1,775	4.0	2.8	8.0	73	22	34	44
			10-11	122	80	142	1,778	5.0	3.3	5.8	73	27	41	32
			12-16	73	73	175	1,650	3.0	3.0	7.2	67	18	40	42
W. O'B.	17.7	16.0	1-7	56	56	168	1,395	3.2	3.2	9.5	79	17	36	47
			8-9	71	56	167	1,458	4.0	3.2	9.4	82	20	34	46
			10-11	89	66	127	1,457	5.0	3.7	7.2	82	24	41	35
			12-16	53	53	177	1,395	3.0	3.0	10.0	79	15	34	51
E. S.	21.3	23.4	1-7	64	64	150	1,433	3.0	3.0	7.0	67	18	40	42
			8-9	85	64	150	1,516	4.0	3.0	7.0	71	22	38	40
			10-11	107	74	105	1,516	5.0	3.5	4.9	71	28	44	28
			12-16	64	64	150	1,433	3.0	3.0	7.0	67	18	40	42

*Diet taken incompletely during acute infection in period 8.

period, he was given no amino acids intravenously. He developed a fever of 103° F. and a sore throat, but did not appear to be gravely ill. His temperature returned rapidly to normal after taking some aspirin and remained normal all night. Blood culture was sterile. The second day of this period his temperature rose rapidly to 105° F., and at noon the patient was prostrated with a grave illness. While his temperature was rising to a peak of 108° F. by 1:30 P.M., a blood culture was taken, and another at the temperature peak. At the height of his temperature an infusion of 125 c.c. of 25 per cent glucose was given with 1 Gm. of aspirin, followed by a tepid sponge. Within two hours his temperature fell to 103.6° F., and the patient developed a generalized convulsion. Though no information from the blood cultures was available, on clinical grounds the infection appeared to be of hemolytic streptococcus origin, and late in the afternoon neoprontosil intramuscularly was begun. The 2.5 per cent solution was used; 5 c.c. were given every four hours for two doses, and 2.5 c.c. every four hours thereafter. On this day he also received two additional infusions of 20 per cent glucose of 125 c.c. each. The following morning the patient's two blood cultures taken the previous day were reported as positive for hemolytic streptococcus Group A, Type 13 (Lancefield). The first culture contained about 5 colonies per cubic centimeter and the second about 200 colonies per cubic centimeter. Although by the morning of the third day the patient's temperature was down to 102° F., he remained gravely ill. Blood chemistry studies showed a plasma amino nitrogen of only 2.10 mg. per cent; therefore, 10 Gm. of amino acids in 10 per cent solution were given intravenously in addition to 28 Gm. of glucose in 10 per cent solution and 40 c.c. of convalescent human scarlet fever serum. Later in the day, on two occasions, the patient was given an additional 40 c.c. of convalescent scarlet fever serum. The neoprontosil therapy did not result in a satisfactory concentration in the blood, the value being below 1 mg. per cent after twenty-four hours, so the patient was changed on this evening to sulfanilamide by mouth, 0.66 Gm. every four hours for two doses and then 0.33 Gm. every eight hours. The morning of the fourth day his temperature was nearly normal, the blood sulfanilamide concentration was 7 mg. per cent, and the plasma amino acid nitrogen, 2.09 mg. per cent. Ten grams of amino acids in 10 per cent solution, plus 25 Gm. of glucose in 10 per cent solution and 40 c.c. of convalescent serum, were given intravenously. An attempt was made to match the patient for transfusion, but no suitable donor could be found. The patient's blood agglutinated several donors of the same type. His temperature fell gradually to normal, and two days later sulfanilamide therapy was discontinued. Further convalescence was uneventful. During his acute illness the patient was fed a liquid diet with the same caloric, protein, carbohydrate, and fat content as

his regular diet. Except for two days when he was critically ill, this diet was surprisingly well taken. This was made possible by the careful nursing care by Miss E. Glantz and the nurses under her, and the skillful compounding of the diet by Miss M. Rhine and her staff in the diet kitchen. During the remainder of the study the patient had no further illnesses.

Beginning with period eight, the diet of E. S., R. Q., and W. O'B. was increased to 4 Gm. of protein per kilogram of ideal body weight. The patients were kept on this diet for two one-week periods. The protein content of the diets was then increased to 5 Gm. per kilogram for two periods, the first of four days and the second of three days. After this time on the very high diet, the protein content was reduced to 3 Gm. per kilogram where it was maintained for the duration of the study. Because of his severe illness, the diet of J. C. was not increased during these periods. Following restoration of optimal protein diets, a control period of one week elapsed before amino acid administration was resumed. During period 14, 5 Gm. of casein hydrolysate as a 10 per cent solution was given intravenously before breakfast daily for five days. The amino acid solution was mixed with an equal volume of 10 per cent glucose during this period and also whenever administered during period fifteen. During period fifteen, W. O'B. and R. Q. received 5 Gm. each on the fourth and sixth days of the period; E. S. received 10 Gm. on each of these days, and J. C., 15 Gm. on the fourth and 10 Gm. on the sixth day. During the final week another control study was run.

Throughout the study the urea plus ammonia nitrogen of the urine was determined, and its ratio to the nonprotein nitrogen of the urine was calculated.

Except for the above-described illness of J. C., all the children were free from infection and fever throughout the period of study. Fortunately, there was no vomiting of food during the balance study except on a very few occasions, and an equivalent amount of food was immediately re-fed. No corrections in nitrogen balance were necessary for accumulation or loss of edema or elevation of blood nonprotein nitrogen during the study.

RESULTS

No severe reactions followed the intravenous administration of the casein hydrolysate. The patients all developed a marked flush at the beginning of the infusion which persisted throughout the time the injection was being given and for about fifteen to twenty minutes after its conclusion. A sensation of warmth was noted at the same time by the patients. These effects were not altered by the speed of injection. On numerous occasions a sensation of nausea was complained of, and in

several instances this was followed by rather severe retching. In these patients, the development of nausea and vomiting seemed to be related not only to the rate of injection but also to the total amount given. With small doses, e.g., 5 Gm., given slowly, i.e., during thirty minutes, there was little nausea and no vomiting. When this amount was injected within a period of from five to seven minutes, nausea usually developed, but emesis did not always follow. When 10 Gm. or more were given in a twenty-minute period, nausea was common, and frequently there was retching. One patient, W. O'B., always developed retching whenever the total amount administered at any single injection exceeded 6 Gm. This reaction could not be avoided in this patient by very slow injection. J. C., on the other hand, was able to take 15 Gm. at one administration without vomiting, although there was very definite nausea. When the material was given after meals, both of these reactions were exaggerated to such an extent that administration under these conditions had to be stopped. During the period of amino acid injection, the patients felt unusually well and played with great vigor throughout the day. Their appetites remained excellent.

The rise in plasma amino acid nitrogen immediately after injection was quite constant. After 5 Gm. was given on each of two occasions, the plasma amino acid nitrogen for E. S. rose in one instance from 3.47 to 8.28 mg. per cent and on the other occasion from 3.63 to 6.65 mg. per cent. In the latter instance, thirty minutes later the value had dropped to 4.09 mg. per cent. The administration of a like amount to J. C. on each of two occasions was followed by a rise from 3.14 to 8.72 mg. per cent and from 3.30 to 7.83 mg. per cent, which in thirty minutes had decreased to 4.23 mg. per cent. After 10 Gm., the plasma amino acid nitrogen of R. Q. rose from 3.47 to 12.07 mg. per cent, and in W. O'B., from 3.33 to 11.61 mg. per cent. There were no significant changes in the concentration of the blood urea nitrogen nor increased urea excretion in the urine immediately following the injections. Subsequent studies, as yet unpublished, indicate that, within one hour after administration of amino acids intravenously, the blood level has returned to its original value. Although the injected amino acids were retained, there was no decrease in the plasma amino deficit following a series of injections. This absence of effect on the fasting level is shown in Figs. 5 to 8. After a series of injections, the fasting level was somewhat lower on W. O'B. in periods 3 and 14, on E. S. in period 15, on R. Q. in periods 3, 7, and 15. There was a slight rise on W. O'B. in periods 7 and 15, on E. S. in periods 3, 7, and 14, and on J. C. in period 3. Significant but transient rises were seen on J. C. in periods 7 and 15, and in R. Q. in period 14. The variation seen in these periods was no greater than spontaneous variations previously observed in these same patients.

The pigment responsible for the color of the amino acid solution appeared to be immediately and quantitatively excreted in the urine. After an injection, the color of the urine closely approached that of the solution administered, and although we did no careful studies on this pigment, the earlier study on urine nitrogen after amino acid injection indicated that no significant loss of injected nitrogen occurred.

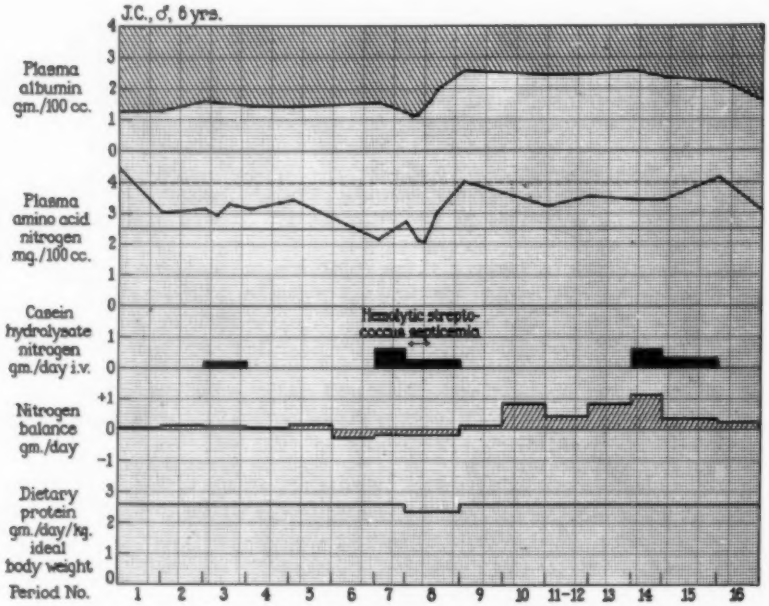
J.C., ♂, 6 yrs.
Plasma albumin gm./100 cc.
Plasma amino acid nitrogen mg./100 cc.
Casein hydrolysate nitrogen gm./day i.v.
Hemolytic streptococcus septicemia
Nitrogen balance gm./day
Dietary protein gm./day/kg. ideal body weight
Period No.
1 2 3 4 5 6 7 8 9 10 11-12 13 14 15 16

Fig. 5.—Summary of nitrogen balance studies on J. C. Note the negative nitrogen balance in period 6, one full week before the first nephrotic crisis. No effects upon the level of plasma amino acids followed injection of casein hydrolysate. Plasma albumin rose parodoxically during period 8, when the patient was on a negative nitrogen balance, and fell through periods 15 and 16, when nitrogen balance was positive. Normal average plasma amino acid nitrogen 4.50 mg. per 100 c.c.

The effects on the nitrogen balance was shown in Table II and Figs. 5 to 8. R. Q. was on a positive nitrogen balance in every period except 13. This period began a lower protein diet than was given in period 12. The excess loss of nitrogen during this period was apparently due to the fact that the patient was not able to attain immediate equilibrium with the lowered protein intake. The small amount of nitrogen lost for the period, however, indicated that she was able to make a fairly rapid adjustment to the diminished intake of nitrogen. On the other hand, the very large positive balances noted in periods 9 and 11 were caused by an increase in dietary protein without allowing an interval to elapse for attaining equilibrium on the higher diet. The maintenance of a positive nitrogen balance

during periods 10 and 12 and failure to excrete an amount of nitrogen during period 13 equivalent to the excess retained during the adjustment periods 9 and 11, indicated that apparently all of the nitrogen retained during the attainment of nitrogen equilibrium on the changed diets was actually assimilated. The administration of amino acids to this patient did not markedly alter the nitrogen balance. W. O'B. was

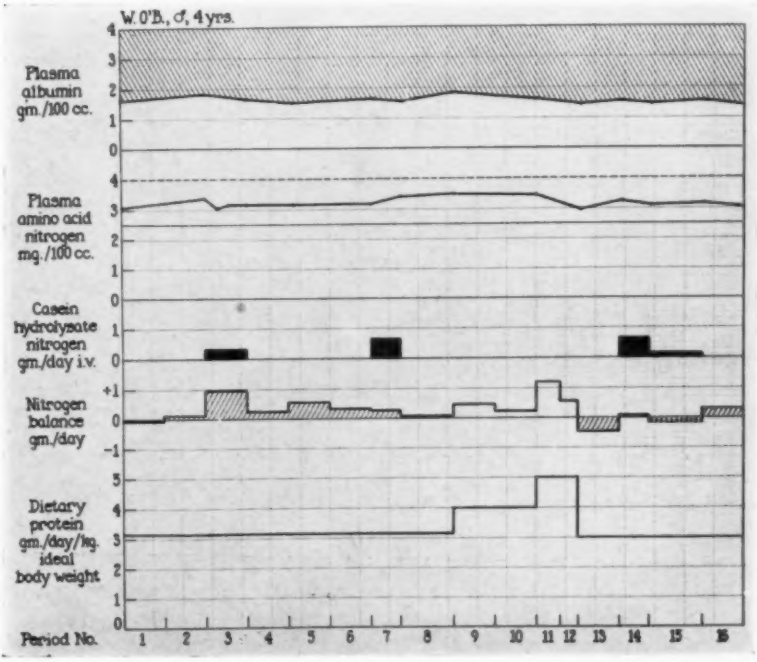
W. O'B., ♂, 4 yrs.
Plasma albumin gm./100 cc.
Plasma amino acid nitrogen mg./100 cc.
Casein hydrolysate nitrogen gm./day i.v.
Nitrogen balance gm./day
Dietary protein gm./day/kg. ideal body weight
Period No.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Fig. 6.—Summary of nitrogen balance studies on W. O'B. Note the constant level of plasma albumin throughout the study although the nitrogen balance was positive throughout thirteen of sixteen periods. Normal average plasma amino acid nitrogen 4.50 mg. per 100 c.c.

on a positive nitrogen balance throughout the study except for periods 1, 13, and 15. The loss of nitrogen during period 13 followed a change in diet to a lower intake and does not represent a true lack of assimilation. The negative balance noted in periods 1 and 15, however, cannot be explained on the basis of dietary changes or infection, but must be a reflection of disturbances in nitrogen assimilation during these periods. The large positive balances for periods 9 and 11 again reflect a change in diet. A smaller amount of nitrogen was retained during these periods and also during periods 10 and 12 by W. O'B. than by R. Q. Again, in W. O'B. no marked effect upon nitrogen assimilation was seen after amino acid administration. The nitrogen balance of E. S. was influenced during periods 9, 11, and 13 by changes in diet. The relatively

large amounts of nitrogen retained during periods 9 and 11 were not lost during periods 10 and 12, and very rapid attainment of equilibrium after changes in the diet is indicated by the very small loss during period 13. This patient showed a more marked response to amino acid administration than did any of the other patients studied. Her nitrogen assimilation increased most markedly during period 7, when the amino acids were given without the simultaneous administration of glucose.

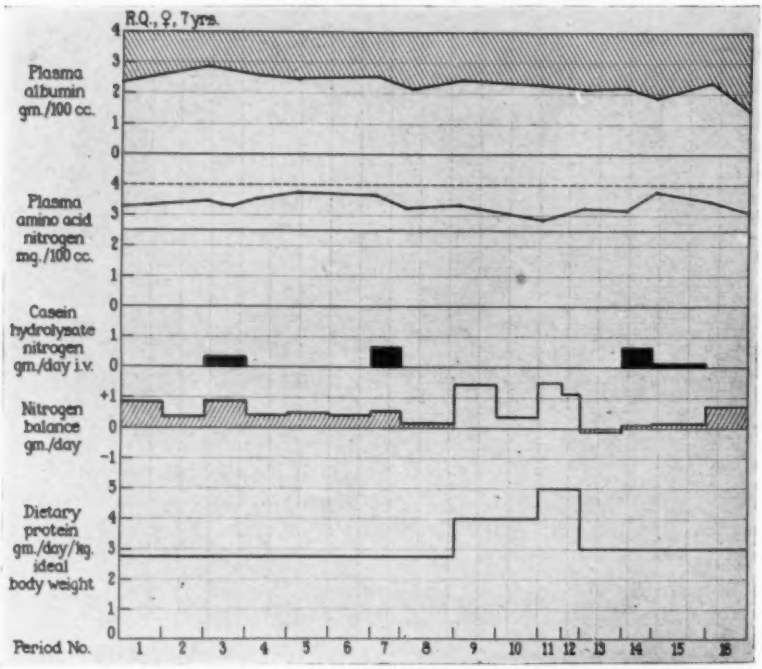
R.Q., ♀, 7 yrs.
Plasma albumin gm./100 cc.
Plasma amino acid nitrogen mg./100 cc.
Casein hydrolysate nitrogen gm./day i.v.
Nitrogen balance gm./day
Dietary protein gm./day/kg. ideal body weight
Period No.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Fig. 7.—Summary of nitrogen balance studies on R. Q. Note the gradual decrease in plasma albumin, although the nitrogen balance was positive. Retention of nitrogen during periods 9 and 11, following changes in protein intake, was indicated by the continuing positive nitrogen balance through periods 14 to 16. Normal average plasma amino acid nitrogen 4.50 mg. per c.c.

The negative nitrogen balance noted during periods 4 and 5 was not due to infection or diet change, but was due to the failure to assimilate nitrogen which is characteristic of nephrotic patients. J. C. was on a positive nitrogen balance, except during periods 6, 7, and 8. The negative nitrogen balance during period 6 preceded a nephrotic crisis which developed the first day of period 7 and another crisis complicated with infection during period 8. The development of a negative nitrogen balance as a characteristic precursor to nephrotic crises has already been described.[16] It is worth noting that there was no increased loss of nitrogen during period 8 as compared with the preceding period, al-

though the patient suffered from a severe infection during this time. The marked positive nitrogen balance after recovery from the crises and infection reflected an improvement in nitrogen assimilation during this interval. The nitrogen balance of this patient was not altered significantly by administration of amino acids.

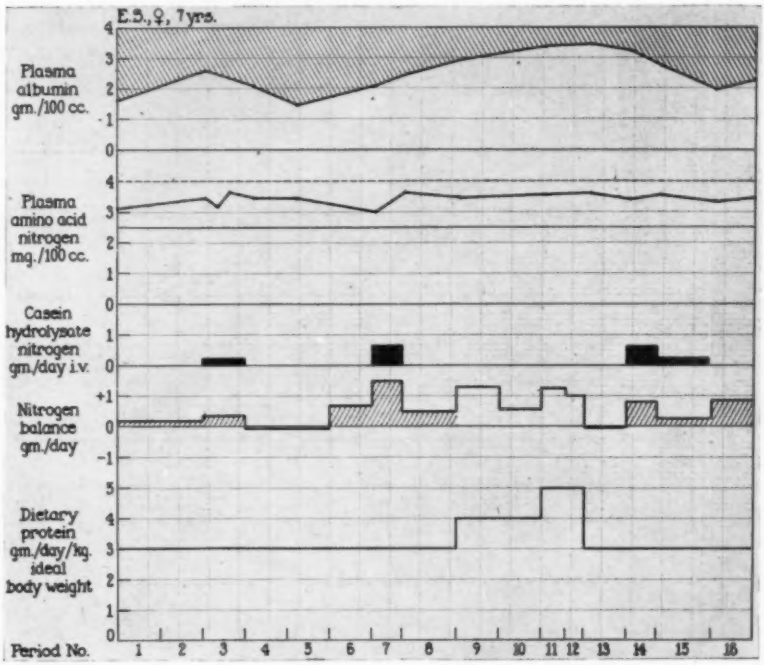
E.S., ♀, 7 yrs.
Plasma albumin gm./100 cc.
Plasma amino acid nitrogen mg./100 cc.
Casein hydrolysate nitrogen gm./day i.v.
Nitrogen balance gm./day
Dietary protein gm./day/kg. ideal body weight
Period No.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Fig. 8.—Summary of nitrogen balance studies on E. S. Note the fall in plasma albumin level during periods 3, 14, and 15, although the patient was on a positive nitrogen balance. Normal average plasma amino acid nitrogen 4.50 mg. per 100 c.c.

No effects upon the level of the plasma proteins nor the degree of proteinuria were noted after amino acid injections. What was more surprising was the failure of the plasma albumin to increase in R. Q. after fifteen weeks in positive nitrogen balance, and the marked improvement in plasma albumin in J. C. during period 8 when he was in negative balance. The fall in plasma albumin seen in E. S. while on a continuously positive nitrogen balance was not expected.

The average value of the urea clearance increased after administration of amino acids in three of the patients, E. S., J. M., and R. Q. (Figs. 1 to 3). There was no obvious effect upon the urea clearance of J. C. (Fig. 4). The increase in urea clearance was noted immediately after the injections were started. From three to five months elapsed following the final amino acid injection before the urea clearances in these patients

TABLE II

SUMMARY OF NITROGEN BALANCE DATA ON FOUR PATIENTS TO WHOM THE CASEIN HYDROLYSATE WAS GIVEN INTRAVENOUSLY AS A 10 PER CENT SOLUTION

PATIENT	PERIOD	NUMBER OF DAYS	DAILY AVERAGE						
			DIETARY NITROGEN INTAKE (GM.) A	CASEIN HYDROLYSATE NITROGEN (GM.) B	URINE NONPROTEIN NITROGEN (GM.) C	URINE PROTEIN NITROGEN (GM.) D	STOOL NITROGEN (GM.) E	BALANCE (GM.) (A + B) − (C + D + E)	RATIO IN URINE OF UREA N + NH_2 N / NONPROTEIN N
J. C.	1	7	7.200		5.330	0.736	1.086	0.048	–
	2	7	7.200		5.150	0.768	1.125	0.157	0.86
	3	7	7.200	0.219[1]	5.248	0.832	1.211	0.128	0.86
	4	7	7.200		5.303	0.736	1.126	0.035	0.84
	5	7	7.200		5.317	0.624	1.077	0.182	–
	6	7	7.200		5.405	0.784	1.291	−0.272	0.87
	7	5	7.200	0.640[2]	5.899	1.008	1.094	−0.161	0.85
	8	9	6.364	0.284[1]	4.803	1.104	1.108	−0.182[3]	0.81
	9	7	7.200		5.264	0.640	1.160	0.136	–
	10	7	7.200		4.496	0.688	1.162	0.854	–
	11-12	7	7.200		4.935	0.608	1.206	0.451	0.86
	13	7	7.200		4.795	0.544	0.996	0.865	0.88
	14	5	7.200	0.640[1]	5.040	0.672	0.987	1.141	0.85
	15	9	7.200	0.333[4]	5.307	0.800	1.049	0.377	0.86
	16	7	7.200		5.307	0.672	1.006	0.215	0.88
W. O'B.	1	7	8.960		7.678	0.112	1.247	−0.077	–
	2	7	8.960		7.568	0.224	1.056	0.112	0.89
	3	7	8.960	0.324[1]	6.972	0.272	1.090	0.950	0.94
	4	7	8.960		7.249	0.384	1.069	0.258	0.86
	5	7	8.960		7.089	0.224	1.085	0.562	–
	6	7	8.960		7.467	0.132	1.014	0.347	0.89
	7	5	8.960	0.640[2]	8.043	0.163	1.110	0.284	0.88
	8	9	8.960		7.575	0.256	1.038	0.091	0.89
	9	7	11.360		9.421	0.384	1.068	0.487	–
	10	7	11.360		9.399	0.312	1.434	0.215	–
	11	4	14.240		11.586	0.288	1.159	1.207	0.91
	12	3	14.240		12.062	0.400	1.228	0.550	0.90
	13	7	8.480		7.679	0.288	0.998	−0.485	0.89
	14	5	8.480	0.640[1]	7.362	0.430	1.253	0.075	0.89
	15	9	8.480	0.133[4]	7.493	0.304	0.984	−0.168	0.89
	16	7	8.480		6.956	0.240	0.980	0.304	0.89

R. Q.	1	7	10.720		8.251	0.464	1.151	0.854	-
	2	7	10.720		8.414	0.576	1.347	0.383	0.93
	3	7	10.720	0.320[1]	8.654	0.432	1.080	0.880	0.90
	4	7	10.720		8.465	0.592	1.224	0.439	0.86
	5	7	10.720		8.672	0.426	1.116	0.506	-
	6	7	10.720		8.811	0.416	1.070	0.423	0.85
	7	5	10.720	0.640[2]	9.031	0.464	1.293	0.572	0.89
	8	9	10.720		8.504	0.576	1.464	0.176	0.91
	9	7	15.680		12.036	0.688	1.535	1.421	-
	10	7	15.680		13.046	0.592	1.648	0.394	-
	11	4	19.520		15.517	0.832	1.677	1.494	0.92
	12	3	19.520		15.616	0.816	1.945	1.143	0.91
	13	7	11.680		9.672	0.704	1.414	-0.110	0.90
	14	5	11.680	0.640[1]	9.907	1.003	1.305	0.105	0.89
	15	9	11.680	0.133[4]	9.568	0.800	1.280	0.165	0.88
	16	7	11.680		9.048	0.784	1.146	0.702	0.90
E. S.	1	7	10.240		8.602	0.181	1.275	0.182	-
	2	7	10.240		8.518	0.096	1.439	0.187	0.88
	3	7	10.240	0.230[1]	8.913	0.288	0.921	0.349	0.88
	4	7	10.240		8.298	0.688	1.345	-0.091	0.86
	5	7	10.240		8.073	0.864	1.390	-0.087	-
	6	7	10.240		7.908	0.336	1.304	0.692	0.88
	7	5	10.240	0.640[2]	8.183	0.139	1.111	1.492	0.88
	8	9	10.240		8.591	0.000	1.167	0.482	0.89
	9	7	13.600		10.737	0.000	1.564	1.299	0.93
	10	7	13.600		11.652	0.040	1.337	0.571	-
	11	4	17.120		14.447	0.000	1.411	1.262	0.90
	12	3	17.120		14.796	0.030	1.288	1.006	0.90
	13	7	10.240		8.888	0.136	1.242	-0.026	0.89
	14	5	10.240	0.640[1]	8.661	0.239	1.177	0.803	0.89
	15	9	10.240	0.267[4]	8.546	0.432	1.271	0.258	0.88
	16	7	10.240		8.093	0.142	1.160	0.845	0.90

[1]Equal volume of 10 per cent glucose given simultaneously.
[2]No glucose administered simultaneously.
[3]Total nitrogen intake includes 1.665 Gm. of nitrogen in convalescent serum given during acute infection with hemolytic streptococcus.
[4]Given with glucose one hour after meals.

returned to their pre-injection level. The increase in clearance was not due to a decrease in blood urea nitrogen during the injection periods, since this value did not change appreciably. There was no water diuresis following injection, although the average total urine output during the injection periods was somewhat higher than during rest periods. The same average urine volume increase has been obtained in these patients by administration of water alone. Under these circumstances, no change in the clearance level was observed.

The administration of amino acids did not change the proportion of urea plus ammonia nitrogen in the urine. The ratios remained remarkably constant in all four patients.

DISCUSSION

The marked retention of nitrogen was not expected on the diets which contained in excess of 3 Gm. of protein per kilogram of ideal body weight. In a previous study of nitrogen assimilation in five nephrotic children, both the relative and absolute assimilation of nitrogen decreased when more than 3 Gm. of protein per kilogram was fed.[2] Subsequent experience in this clinic with very high protein diets for these children has substantiated these observations. Maroney and Johnston[17] found decreased assimilation of nitrogen in normal children when more than 20 per cent of the total calories were furnished by protein. On the other hand, the normal child can readily maintain himself in positive nitrogen balance with only 2 Gm. of protein per kilogram, while the nephrotic child requires at least 2.5 Gm. of protein per kilogram. The inability of the nephrotic child to maintain himself in nitrogen equilibrium on a diet adequate for a normal child cannot be accounted for on the basis of nitrogen lost as protein in the urine. Increase of minimal nitrogen requirement in these patients simulates in many ways the increased requirements of nonnephrotic patients with fever or other intoxication. Since the behavior of the nephrotic child in regard to nitrogen assimilation parallels that observed in toxic conditions, for convenience, such states, in which a negative nitrogen balance exists in a nephrotic patient with an adequate intake of dietary protein, may be characterized as those of "toxic" nitrogen metabolism, with the important reservation that *no assumption is made concerning the cause of the accelerated nitrogen excretion.*

Unpublished data obtained by us on nonnephrotic patients with pneumonia and bronchiectasis indicated that, under such well-recognized toxic conditions, hypoaminoacidemia was not uncommon. Thus, the hypoaminoacidemia and nitrogen wasting seen in nephrotic patients become different facets of "toxic" nitrogen metabolism. Although the administration of amino acids to these nephrotic patients did not decrease the minimal nitrogen requirements nor dramatically reverse a

patient from the "toxic" to the nontoxic type of nitrogen metabolism, this would be expected since the level of plasma amino acids remained subnormal, and, hence, the nitrogen metabolism remained of the "toxic" type with increased maintenance requirements. The simultaneous administration of glucose did not enhance the effects of the amino acids.

On the other hand, the amino acid injections apparently increased the capacity to assimilate nitrogen to an extent sufficient to overcome the toxic effects of a high protein diet. At the end of three weeks' feeding of the high protein diets, clinical effects of toxicity were noted in increasing pallor and loss of appetite. During the first two weeks, however, the effects of amino acid injections given one full week prior to feeding the high protein diets remained dominant. This assumption of continuing effect for a period of time after injection is not unreasonable, as it was pointed out in a discussion of the effects upon the urea clearance that the clearance remained elevated for from three to five months after the injections were discontinued.

Following the high protein diets there was a sharp drop in the plasma albumin level of E. S., although she remained on a positive balance. Her rapid subsequent recovery when the optimal diet was restored and the fact that she made a complete recovery from her disease in the next two months indicate that the regulation of protein level in the blood of nephrotic patients may be one of the first mechanisms deranged in the disease. This partial independence of the plasma albumin level in relation to total nitrogen exchange was shown also by J. C., who exhibited a rise in plasma albumin during period 8 while on a negative nitrogen balance and a subsequent gradual fall during the last few periods while on a positive nitrogen balance. Since it is thus apparent that, over short intervals, the plasma albumin level may move in a direction counter to the general nitrogen assimilation, failure to find improvement in plasma albumin levels immediately after injection sheds no light on the utilization of the injected amino acids. That they shared the fate of dietary protein was indicated by the constancy of the ratio of urea plus ammonia nitrogen to total nonprotein nitrogen in the urine. Presumably, nitrogen retained was first used to restore depleted tissue proteins and to satisfy growth requirements, and only under unusual circumstances, such as prevailed in J. C. during and immediately after his hemolytic streptococcus infection, was the retained nitrogen diverted to the manufacture of plasma proteins. No deductions can be drawn from these studies as to the nutritional adequacy of the amino acid mixture used since no attempt was made to use this as the sole or major portion of nitrogen supplied.

The rise of the urea clearance following amino acid injection seemed to correspond to the rise previously observed in this type of patient

when the diet was changed from a low to a high protein content.[18] The same changes cannot be induced by feeding urea. In a study on dogs, Van Slyke, Rhoads, Hiller, and Alving[19] found the change in urea clearance observed when the protein in the diet was increased to be due to an increased renal blood flow. It would appear that the stimulating factor under these circumstances may have been the increased supply of amino acids. Further studies on this point are at present under way in this clinic.

CONCLUSIONS

Four nephrotic children, two boys, aged 4 and 6 years, and two girls, each aged 7 years, have been observed on a nitrogen balance study for fifteen consecutive weeks.

Procedures used in dissolving and storing a suitable casein hydrolysate for intravenous use were described.

The intravenous administration of amino acids as a casein hydrolysate caused flushing of the skin and a sensation of warmth. When the infusions were given rapidly or large quantities administered, in addition to the above reactions, nausea and vomiting were common. No febrile reactions were encountered.

Nitrogen given as intravenous amino acids was assimilated and retained as well as, or better than, similar amounts of nitrogen fed as protein. After amino acid injections, the capacity of nephrotic patients to assimilate high protein diets was markedly increased over that previously observed. Increased effects of amino acids were not obtained by the simultaneous administration of glucose.

The injections had no effect upon the ratio of urea plus ammonia nitrogen to nonprotein nitrogen in the urine, plasma protein level, or fasting plasma amino acid level.

In three of the four patients the administration of amino acid intravenously produced an increase in the urea clearance which persisted for from three to five months after injections had been discontinued.

The nature of the inability of nephrotic patients to assimilate nitrogen was discussed.

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ACACIA THERAPY IN A CHILD WITH NEPHROSIS

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IN 1933, Hartmann and co-workers[1] reported the successful use of acacia intravenously in the treatment of children with nephrosis. Recently, Lepore,[2] Landis,[3] Barach and Boyd,[4] and Shelburne[5] reported temporary improvement in patients with edema and lowered serum protein. The purpose of the acacia is to increase the colloid osmotic pressure of the blood to compensate for the decrease caused by the lowered serum protein. Several observers have noted adverse effects of acacia. Dick, Warweg, and Andersch[6] made the following conclusions from their study on both human beings and dogs: acacia administration resulted in (1) a marked lowering of the serum protein; (2) a deposition of acacia in the liver, bone marrow, lymph nodes, lungs, kidneys, and spleen; and (3) only a transitory or slight effect upon edema.

Jackson and Frayser,[7] continuing these studies on dogs, found that: (1) the reduction in serum protein following the administration of acacia intravenously was not a simple dilution effect; (2) the albumin, globulin, and fibrinogen fractions all decreased slowly and regenerated; and (3) the cholesterol was reduced to about one-half the normal value, with a slow increase tending to parallel the increase of protein. Dick and his co-workers[6] and Jackson and Frayser[7] concluded that the intravenous administration of acacia is contraindicated in nephrosis. Andersch and Gibson[8] found deposition of large amounts of acacia in the livers of rabbits and dogs following its intravenous injection. Studdiford[9] confirmed these findings by three necropsies of patients who had received acacia for postpartum hemorrhage; he believes that acacia leads to damage of the liver and is dangerous. Hall[10] reported a change in the glucose and galactose tolerance curves following the intravenous administration of acacia to dogs, which he interprets as evidence of damage to the carbohydrate and serum protein metabolic functions of the liver. Heckel and co-workers[11] showed that a lowered plasma protein concentration following single injections of acacia in normal dogs was due, in part, to dilution and, in greater part, to actual decrease in total circulating protein. These authors conclude that clinical use of acacia for intravenous injections is not without danger. Fukuhara and Hiratsuka[12] reported a series of observations covering only three hours after the intravenous administration of acacia to normal rabbits and to rabbits with liver and kidney damage. These authors observed that the effect of acacia on colloid osmotic pressure of blood was of short dura-

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tion in all the animals and that the effect was less in the rabbits with liver or kidney damage. They noted also a lowering of the plasma protein and hemoglobin which was more marked in the rabbits with liver or kidney damage. Austin and McGuinness[13] discussed the added danger of circulatory failure produced by increase in blood volume following the intravenous administration of acacia.

This report describes briefly the course of nephrosis and summarizes the autopsy findings in one of the patients reported by Dick, Warweg, and Andersch.[6]

D. S., a boy, aged 6 years, came under observation June 11, 1932, because of swelling of the entire body. The onset had occurred four months previously with an upper respiratory infection. Edema appeared in the face and ankles two weeks later, spreading rapidly to the remainder of the body and becoming progressively worse.

Examination showed generalized edema, subacute faucial and pharyngeal tonsillitis, mild sinusitis, and pallor. The blood pressure was 96/60; the urine showed a fairly large amount of albumin and casts, but no blood. The hemoglobin was 70 per cent (Tallqvist); red blood count, 2,450,000; white blood count, 6,150, with a normal differential count. The blood Wassermann reaction was negative. The serum protein was 4.7 Gm. per 100 c.c.; nonprotein nitrogen, 53 mg. per 100 c.c.; and cholesterol, 320 Gm. per 100 c.c.

A high protein diet was prescribed and its intake supervised. The infection of the upper respiratory tract was treated conservatively. Blood transfusions were given frequently. Concurrent with this regimen of treatment, the edema increased. To combat the edema, acacia was given intravenously, approximately 1 Gm. for each kilogram of body weight, in concentrations varying from 6 to 15 per cent. Ampoules of 30 per cent acacia with 4.5 per cent sodium chloride diluted with distilled water were used. The edema varied in degree following its use, decreasing at first, but later showing little alteration, even after repeated generous dosages of acacia. Thyroid and salyrgan had little effect. During a period of six months of acacia therapy, the liver enlarged almost to the umbilicus and became very tender. During this period of acacia administration, the serum protein fell from 4.7 Gm. per 100 c.c. to 1.5 Gm. per 100 c.c. Because of the enlarging liver, acacia therapy was discontinued after a total of 705 Gm. had been given intravenously. With subsequent repeated blood transfusions and treatment of the infection of the upper respiratory tract, gradual improvement was noted. The level of total serum protein remained alarmingly low, below 3 Gm. per 100 c.c., for many months. Not until October, 1933, ten months after the boy was last given acacia, did the serum protein reach the level of 4 Gm. per 100 c.c.

By Dec. 12, 1934, two and one-half years later, the patient was edema-free and had no symptoms. The liver was still enlarged so that it extended three finger-breadths below the costal margin. The serum protein was 5.3 Gm. per 100 c.c., but the albumin fraction was only 1.8 Gm. per 100 c.c., and the globulin, 3.6 Gm. per 100 c.c. The urine still contained a trace of albumin, but no casts or red blood cells.

During the next few years, the child was brought to the hospital many times. Physical examination always revealed an enlarged liver, a questionable enlargement of the heart, and varying degrees of edema. Acute upper respiratory infections and pansinusitis were commonly present. These were treated in the otolaryngology department by various procedures, including tonsillectomy, adenoidectomy, and sinus washings. The blood pressure remained essentially normal throughout. There

was no acidosis at any time. Kidney function, urea clearance, and glucose tolerance tests revealed no significant abnormal findings. The red blood count remained about 4,000,000 throughout this course.

During these various periods of observation, the boy received many blood transfusions, but at no time did his total serum protein reach a level higher than 5.86 Gm. per 100 c.c. The total serum protein varied from the lowest value of 3.2 Gm. to the highest value of 5.86 Gm. per 100 c.c. The serum albumin levels varied from a minimum of 0.3 Gm. to a maximum of 3.3 Gm. per 100 c.c., and the serum globulin varied from 1.7 Gm. to 3.25 Gm. per 100 c.c. Except for a few

TABLE I

DATE OF OBSERVATION	TOTAL SERUM PROTEIN (GM./100 C.C.)	SERUM ALBUMIN (GM./100 C.C.)	SERUM GLOBULIN (GM./100 C.C.)	SERUM FIBRINOGEN (GM./100 C.C.)	CHOLESTEROL (MG./100 C.C.)	WEIGHT (POUNDS)	EDEMA
6/13/32	4.7				320	54	+
10/26/32	1.35	.75	.60				
12/ 6/32					118.5		
1/22/33	2.6					47½	
2/23/33	2.6				400	43	+
6/ 5/33	2.4				307	56	+
6/12/33	2.7				214	50	
10/ 2/33	4.1				320	50	+
2/ 3/34	5.0	1.7	3.1	.2	296	55	±
6/11/34	3.62				571	59½	+
6/19/34	4.86	1.94	2.92		400	55	
8/21/34	5.17	1.5	3.24	.43	625	57	–
12/11/34	5.34	1.75	3.59		351	56½	+
4/16/35	5.6	2.8	2.8		151	60½	–
6/ 8/35	3.2	.6	2.6		800	73	+
7/ 2/35	4.6	2.3	2.3			58	
8/10/35	4.2	0.5	3.1	.5	638	81	+
8/30/35	3.9	0.9	3.0		800	57	
11/29/35	5.86	2.83	3.03		400	61½	+
2/12/37	4.2	1.5	2.0	.6	667	77½	+
3/ 2/37	4.7	1.3	2.8	.1		68½	
4/21/37	4.75	1.99	1.95	.81	204		
5/28/37	5.7	3.3	1.7	.7	500	65¾	
8/19/37	3.9	.9	2.6	.4	570	71¼	+
10/28/37	5.4	1.9	2.8	.7			
12/28/37	4.3	1.5	2.3	.6	800		
2/21/38	5.4	2.0	2.7	.7	555	65¼	
5/19/38	4.4	.3	2.9	1.2	930	79½	+
6/ 4/38	5.4	1.0	3.25	1.15	657	67	
7/ 4/38	4.1	.8	2.0	1.3	520	84	+

occasions, the cholesterol value remained high throughout this course, the highest value being 930 mg., and the lowest value being 118 mg., per 100 c.c., immediately following acacia administration. Laboratory data are shown in Table I. In addition to the transfusions, the boy at various times received 50 per cent solutions of sucrose intravenously, and ammonium chloride, thyroid, theocine, liver extract, and digitalis by mouth. His diet averaged from 5.5 to 5.8 Gm. of protein for each kilogram of body weight; varying restrictions were placed upon the amount of salt added to the food. The longest single period wherein the boy remained free from disturbing symptoms was from November, 1935, to February, 1937, a period of fourteen months. In February, 1937, the child was again edematous. The total plasma protein was 4.2 Gm. per 100 c.c., but the albumin fraction was only 1.5 Gm. per 100 c.c. By May, 1937, however, the plasma albumin had increased to 3.3 Gm. per 100 c.c., the highest value ever noted for his blood.

In July, 1938, the boy was admitted in a premoribund state. At this time, he was severely edematous and had pulmonary congestion. Therapy was of no avail. He died about thirty-six hours after admission, with cardiac and respiratory failure. A post-mortem examination was carried out, and the following anatomic diagnoses were made: subacute glomerular nephritis with nephrosis, generalized anasarca, pneumococcic peritonitis, pneumococcic empyema, right, atelectasis of lower lobe of the right lung, acacia deposits in the liver (microscopic), aortic sclerosis with fatty deposits in intima, cholelithiasis, acute pancreatitis secondary to peritonitis, septic spleen, and left-sided bronchopneumonia. The peritoneal fluid contained 169 mg. of protein and a trace of cholesterol in each 100 c.c.

The acacia deposits amounted to 50.3 Gm. in the liver, 2.85 Gm. in the spleen, and 0.07 Gm. in the left kidney, making a total of 53.2 Gm. in the three organs. This represents 7.55 per cent of the total 705 Gm. which was administered in 1932.

This report proves that considerable amounts of acacia remain deposited in the parenchymatous tissues of the body for years after its intravenous administration. Of the total amount administered, 7.1 per cent was recovered from the liver, 0.4 per cent from the spleen, and 0.05 per cent from one kidney six years after administration. During these six years, the child was unable to increase the serum protein to the normal level, despite the fact that, for one period of fourteen months, he remained essentially free from serious recurrences of the nephrosis.

It is our belief that the ultimate recovery of the nephrotic patient is dependent upon his ability to restore his level of serum protein to normal. The acacia seems to hinder protein synthesis. The interference with the serum protein metabolism lasting over a considerable period of time greatly overweighs the transitory benefit resulting from the intravenous use of large doses of acacia. The lowering of the cholesterol value, often used as a favorable prognostic index, is to a great extent an artifact when it occurs after acacia administration.

The fatal course of the disease in this patient may not have a direct relationship to the acacia therapy, but the acacia deposited in the liver may well have interfered with serum protein regeneration.

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SYNTHESIZED, PROCESSED, AND NATURAL SOURCES OF VITAMIN C IN THE MINERAL METABOLISM OF NORMAL CHILDREN

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THE fact that certain fruits have specific nutritive advantages in a general mixed diet has placed them in the category of the so-called "protective foods."[1] Oranges have been shown to possess nutrients which are essential for healthful growth of infants and children[2-5] and to stimulate a favorable metabolic response.[6, 7] Because of these and other characteristics of fruits, Sherman[8] has cogently stated:

> "It is high time for students of food and nutrition to teach confidently that the purchase of fruit is no longer to be regarded as a luxury. It is an investment in health or in higher health. True, there are some fruits whose acids still require investigation; but many fruits, including apples, bananas, cantaloupe, grapefruit, lemons, oranges, peaches, pears, we may feel confident that even in liberal quantities their organic acids will be well burned in the body and that the eating of more of such fruits will contribute to our nutritional health in several ways."

What are the constituents of the orange which give it its nutritive value over and beyond its vitamin content? And, do these constituents change the course of nitrogen and mineral metabolism to effect the nutritive advantages? Credit has been given to the alkaline-ash value of the orange, which provides a substantial excess of positive minerals, for increased growth of infants[2, 3] and children,[4-6] and, thereby, according to some investigators, augmenting calcium metabolism[6] and contributing to the neutralization of the dietary acid residues from meats and cereals by increasing the pH and the organic acids of the urine and diminishing the ammonia.[9-11] Others have attributed the nutritional advantages of oranges to an increased intake of citric acid, which seems to have nutritional and metabolic significance, according to recent studies;[11-13] to a stimulation of gastric flow, thereby increasing the bactericidal power of the stomach, and to its buffer value;[14, 15] to its content of vitamin C, necessary for development of

From the Research Laboratory of the Children's Fund of Michigan in cooperation with The Methodist Children's Village, Detroit.

sound teeth and their resistance to decay;[16, 17] to increased nitrogen utilization;[18, 19] and to increased mineral utilization in scorbutic individuals.[20-22] On the other hand, Rose and Borgeson[23] observed that sixty children between the ages of 1 and 6 years who were maintained on a low cost diet for twenty-one months showed no difference in growth, general health, hemoglobin, and red cell counts when the diet was supplemented with orange.

The present investigation deals with the chemical growth and nutrition of normal children as affected by supplementing their adequate daily mixed diet containing 50 c.c. of an orange-lemon preparation with 20 mg. of ascorbic acid and by substituting the same amount of fresh orange juice for the orange-lemon preparation. The effects of the diet alterations have been sought in the subjects' retentions of nitrogen and positive (calcium, magnesium, sodium and potassium) and negative (phosphorus, chlorine, sulfur) minerals, and other physiologic reactions.

EXPERIMENTAL DATA

Six children, from 5 to 8 years of age (two girls, four boys), who were among the subjects of extensive investigations of growth, provided the material for this study.* They lived together in a home unit in the Methodist Children's Village in Detroit; these children were given every opportunity for unhampered social and physical development. They attended school in the Village and played outdoors during the daylight hours whenever the weather permitted. Two housemothers administered to their emotional needs and managed the children; three young women trained in nutrition and dietetics quantitatively prepared and served the food and collected all metabolic specimens. The food and metabolic specimens were chemically analyzed in the Research Laboratory of the Children's Fund of Michigan.†

The children's diets were composed of twenty-one common foods‡ known to be good for children, and the quantities were adjusted to meet the requirements of the individual person's age, size, and activity. Previous to initiation of the metabolic investigation, well-filled calcium stores for all the children were assured by a prefeeding

*The complete investigation of *The Chemistry of Growth and Nutrition in Childhood* will be published in monograph form and will consider the results obtained from 598 five-day metabolic balances and many additional related clinical and chemical observations upon normal children. Space does not permit details of the metabolic procedures and chemical methods, but these may be obtained from the authors prior to release of the monograph. Dr. Marsh W. Poole kindly gave pediatric service for the children.

†The difficulties inherent in obtaining accurate analytic values for minerals lost through the skin preclude determination of this factor coincident with observations of normal growing children under near-natural conditions. While retentions calculated from chemical analyses of intake, urine, and feces include skin excretion, which primarily contains sodium, potassium, and chlorine, the controlled conditions of investigation would produce a consistent influence from this factor, greatly reduced by the fact that the studies were carried on during the time from October through February.

‡The mixed diet contained the following foods: apple, banana, lean beef, white and whole-wheat bread, shredded wheat, cabbage, carrots, American cheese, eggs, lettuce, milk, orange juice, peanut butter, potato, spinach, tomato juice, graham crackers, butter, sugar, and salt. Distilled water was used for cooking and drinking.

TABLE I

CHANGES IN NITROGEN AND MINERAL ION BALANCES DURING PERIODS OF ADDITIONAL INTAKE OF 20 MG. OF ASCORBIC ACID AND FROM SUBSTITUTION OF FRESH ORANGE JUICE FOR ORANGE-LEMON PREPARATION

	OBSERVATION PERIOD (DAYS)	TOTAL ENERGY INTAKE (CAL./KG.)	LAXATION RATE*	NITROGEN		MINERAL ASH-VALUES OF INTAKE				ION BALANCES IN EXCRETA†		RETENTION OF MINERAL IONS			
				INTAKE (MG./KG.)	RETENTION (MG./KG.)	TOTAL (MEQ./KG.)	POSITIVE (MEQ./KG.)	NEGATIVE (MEQ./KG.)	ALKALINE-ASH VALUES (MEQ./KG.)	URINE (MEQ./KG.)	FECES (MEQ./KG.)	TOTAL (MEQ./KG.)	CATIONS (MEQ./KG.)	ANIONS (MEQ./KG.)	EXCESS IONS† (MEQ./KG.)
B. M. (female)															
Pre-experimental	30	96	2.0	549	26	22.32	11.96	10.36	1.60	0.36-	1.75+	1.87	1.04	0.83	0.21+
Ascorbic acid added	25	94	1.8	533	21	21.69	11.62	10.07	1.55	0.03-	1.38+	1.98	1.09	0.89	0.20+
P. W. (female)															
Pre-experimental	25	93	1.2	495	36	20.77	10.93	9.84	1.10	0.12+	1.23+	2.15	0.95	1.20	0.25-
Ascorbic acid added	25	88	1.1	467	52	19.57	10.30	9.27	1.03	0.07-	1.32+	1.60	0.69	0.91	0.22-
F. C. (male)															
Pre-experimental	40	88	1.8	466	18	19.51	10.27	9.24	1.03	0.02+	1.31+	1.86	0.78	1.08	0.30-
Ascorbic acid added	25	87	1.3	458	21	19.21	10.11	9.10	1.01	0.08-	0.95+	1.42	0.78	0.64	0.14+
Orange-lemon preparation	35	87	1.4	478	4	19.41	10.06	9.35	0.71	0.67-	1.25+	1.18	0.66	0.52	0.13+
Fresh orange juice‡	15	85	1.5	441	28	18.18	9.55	8.63	0.91	0.55-	0.89+	1.31	0.94	0.37	0.57+
H. H. (male)															
Pre-experimental	40	93	2.4	489	20	20.50	10.79	9.71	1.08	0.04-	1.24+	1.72	0.76	0.96	0.20-
Ascorbic acid added	25	93	1.8	489	16	20.51	10.80	9.71	1.08	0.03-	1.04+	1.32	0.70	0.62	0.07+
Orange-lemon preparation	35	90	1.7	497	4	20.19	10.46	9.73	0.73	0.62-	1.21+	1.14	0.64	0.50	0.14+
Fresh orange juice‡	15	93	1.5	484	13	19.94	10.47	9.47	1.00	0.64-	1.00+	1.05	0.85	0.20	0.65+

D. P. (male)															
Orange-lemon preparation	25	82	1.3	441	5	18.58	9.77	8.81	0.96	0.48⁻	1.16⁺	1.76	1.02	0.74	0.28⁺
Fresh orange juice§	15	79	1.5	432	15	18.43	9.79	8.64	1.15	0.82⁻	1.07⁺	2.04	1.47	0.57	0.90⁺
W. P. (male)															
Orange-lemon preparation	25	93	1.8	497	34	20.96	11.02	9.94	1.08	1.04⁻	1.85⁺	1.57	0.92	0.65	0.28⁺
Fresh orange juice§	15	90	1.6	491	48	20.93	11.12	9.81	1.31	1.13⁻	1.62⁺	1.82	1.32	0.50	0.82⁺
Pre-experimental	135	Means		496	24	20.66	10.92	9.74	1.18	0.04⁻	1.37⁺	1.88	0.86	1.01	0.15⁻
		± SE_m¶		±6	±3	±0.20	±0.12	±0.08	±0.04	±0.05	±0.06	±0.11	±0.07	±0.06	±0.07
Ascorbic acid added	100	Means		487	28	20.25	10.71	9.54	1.17	0.05⁻	1.17⁺	1.58	0.81	0.76	0.05⁺
		± SE_m¶		±7	±4	±0.22	±0.14	±0.09	±0.05	±0.05	±0.07	±0.11	±0.07	±0.06	±0.07
Orange-lemon preparation	120	Means		480	10	19.79	10.32	9.47	0.85	0.70⁻	1.35⁺	1.37	0.78	0.59	0.20⁺
		± SE_m¶		±5	±3	±0.18	±0.09	±0.08	±0.03	±0.06	±0.09	±0.14	±0.08	±0.07	±0.07
Fresh orange juice	60	Means		462	26	19.37	10.23	9.14	1.09	0.78⁻	1.14⁺	1.55	1.14	0.41	0.74⁺
		± SE_m¶		±8	±5	±0.34	±0.18	±0.16	±0.05	±0.09	±0.09	±0.19	±0.10	±0.10	±0.08

Initial ages, weights, and recumbent lengths of the subjects were: B.M., 63 months, 15.99 kg., 103.6 cm.; P.W., 78 months, 20.55 kg., 117.9 cm.; F.C., 79 months, 21.27 kg., 119.3 cm.; H.H., 85 months, 20.36 kg., 119.9 cm.; D.P. 102 months, 27.82 kg., 138.5 cm.; W.P., 100 months, 24.50 kg., 120.2 cm.

*Defecations per day.

†Excess of cations is shown by a superior plus sign after the figure; anions, by a superior minus sign.

‡Intake increased with 18 Gm. washed butter fat per day.

§Intakes increased with 3 Gm. washed butter fat per day.

¶SE_m represents the standard error of the mean and is the standard deviation divided by the square root of the number of observations.

period of three months in which the children received at least one quart of milk per day and generous amounts of summer sunshine. To further reduce the number of variables, the subjects were observed continuously throughout two test periods, each fifteen to forty successive days, for each dietary change. Four children who were receiving 50 c.c. orange-lemon juice preparation* per day during a pre-experimental period were given a daily supplement of 20 mg. of ascorbic acid during a period immediately following. Four children were studied while 50 c.c. orange-lemon juice preparation was included in the daily diet and again when the same amount of fresh orange juice was substituted for the prepared mixture. The mixed diets provided acceptable quantities of known vitamins for all body processes, for, with the diets calculated according to the food type group values presented by Munsell,[27] the subjects daily received from 4,800 to 5,000 International Units of vitamin A, from 280 to 400 I.U. of vitamin B_1, from 1,700 to 2,000 I.U. of vitamin C (exclusive of the 20 mg. ascorbic acid added during one study period), and from 600 to 850 I.U. of vitamin G. Although the vitamin D contents of the diets cannot be calculated, the children were well standardized upon adequate diets, received supplementary amounts of vitamin D from irradiated milk, ranging from 90 to 180 I.U. per day, and they played in the open country where sunshine was available in generous amounts.

Table I presents the nitrogen and positive and negative mineral retentions, together with the age, size, caloric intake, and laxation rate (number of defecations daily). Each child grew during all periods of observation; this was demonstrated by the retention of nitrogen and total mineral ions. When the pre-experimental diet was supplemented with 20 mg. of ascorbic acid per day, there were decreased intakes of calories, nitrogen, and excess positive minerals

*The orange and lemon juice preparation used was employed in an effort to obtain a standardized and more stable product than orange juice which would provide the same quantities of vitamin C—a very desirable accomplishment in metabolic work since the composition of foods is highly variable and oranges are no exception to the rule, even though the fruit is encased in a heavy protective rind. Many investigators had demonstrated the inherent variability in the vitamin C content of the fruit and the losses of the vitamin consequent to juicing, straining, heating, and exposure to the air. Bacharach, Cook, and Smith[24] showed that the range of concentration of ascorbic acid per cubic centimeter of juice of thirty-nine oranges was from 0.22 to 0.89 mg., with an average of 0.51 mg. Similar observations have been made in this laboratory on fresh fruit from the market and in sampling individual fruits in carload lots. During a study with infants,[25] it was found that even iron utensils, such as squeezers and strainers (iron acting as a catalyst in oxidation), reduced the vitamin C content of the juice, in some cases by 50 per cent (unpublished data). For this reason, the fresh orange juice was expressed with glass squeezers and strained through cheese cloth. The juice was extracted in quantities sufficient for a five-day period and placed in bottles containing one day's supply for one child, to avoid exposure to air. Kept in a refrigerator at low temperatures, the juice showed no loss from storage when tested for vitamin C.

Although the vitamin C content was lowered in the juice preparation used in this study, it retained its aroma and flavor, could not be differentiated by taste or appearance from fresh orange juice, and its vitamin C content was much more constant than in the fruit on the general market. The mixture contained some sugar which perhaps was responsible for some of the loss of vitamin C,[24] and citric acid, which contributed to the flavor and was thought to have some nutritive effect, also may have contributed to the reduction.[26] Although the preparation contained 22.6 mg. and the fresh orange juice 52.7 mg. ascorbic acid per 100 c.c., in the amounts given (50 c.c.) the difference was 15 mg. per day.

(alkaline-ash value) per kilogram of body weight, and the laxation rates of all four children were slower. On a unit weight basis, three of the children, who were storing an excess of anions during the pre-experimental period, decreased their daily storage of total minerals but retained larger amounts of cations in relation to anions in response to the ascorbic acid; two of the children (F. C. and H. H.) changed in retentions to an excess of cations. The other child's (B. M.) retention of total minerals was larger during the period of augmented ascorbic acid intake, and she continued to store the same excess of cations. The metabolic readjustment in response to the additional vitamin C is demonstrated by the excess ions excreted in the urine and feces. The three children who retained an excess of anions during the pre-experimental period were excreting an excess of cations in their urine. When the additional vitamin C was available, their urines contained an excess of anions and their retentions tended toward the normal growth situation,[28] an excess retention of cations, although one child (P.W.) continued to retain an excess of anions, accompanied by greater fecal excretion of positive minerals and increased nitrogen retention. While no subject's intake of nitrogen per unit weight was raised, one child (F. C.) increased his daily nitrogen retention (from 18 to 21 mg. per kilogram of body weight) with the administration of the ascorbic acid supplement; two others reduced their retentions (B. M., 26 to 21, and H. H., 20 to 16 mg. per kilogram, respectively). However, these latter changes are scarcely significant because the vitamin C changes in intake were small and the diets at no time were deficient in this essential vitamin; on the contrary, it was given in fairly generous amounts in the mixed diets containing fresh fruits and vegetables.

On a unit weight basis there were lower mean energy (88 to 87 Cal.) and nitrogen (480 to 462) intakes when fresh orange juice was substituted for the orange-lemon preparation, but higher alkaline-ash values for the complete diet (0.85 to 1.09 meq.). Despite the decreased intakes, the fresh orange juice demonstrated significant nutritive advantages in greater average daily retentions of nitrogen, total minerals, total cations, and excess cations. Upon applying the analysis of variance method,[29] in which individual variations, as well as variations due to changes in diet, are considered, the means of the retentions of nitrogen, total cations, and excess cations during the periods of fresh orange juice consumption were significantly different from those during the time that the orange-lemon preparation was given.

Table II demonstrates the metabolic changes which took place in the utilization of the individual mineral elements during the 415 experimental days of the investigations. Since the nutritional state of the subjects, the environment, and the procedures were highly standardized and the responses to the dietary changes were, for the most part, in the same direction, the results have been averaged on a unit

TABLE II

AVERAGE DAILY BALANCES OF INDIVIDUAL POSITIVE AND NEGATIVE MINERALS PER KILOGRAM OF BODY WEIGHT*

	INTAKE	OUTPUT				RETENTION	
		URINE		FECES			
	MILLIGRAMS PER KILOGRAM	MILLIGRAMS PER KILOGRAM	PER CENT OF INTAKE	MILLIGRAMS PER KILOGRAM	PER CENT OF INTAKE	MILLIGRAMS PER KILOGRAM	PER CENT OF INTAKE
Positive Minerals							
Calcium							
Pre-experimental	37.2	3.5	9.4	28.5	76.6	5.2	14.0
Ascorbic acid added	36.6	3.4	9.3	26.1	71.3	7.1	19.4
Orange-lemon preparation	41.2	3.6	8.7	32.6	79.1	5.0	12.2
Fresh orange juice	40.9	3.2	7.8	31.4	76.8	6.3	15.4
Magnesium							
Pre-experimental	14.1	4.6	32.6	8.6	61.0	0.9	6.4
Ascorbic acid added	13.9	4.9	35.2	8.0	57.6	1.0	7.2
Orange-lemon preparation	12.3	3.1	25.2	7.8	63.4	1.4	11.4
Fresh orange juice	12.5	3.3	26.4	6.5	52.0	2.7	21.6
Sodium							
Pre-experimental	101.6	93.6	92.1	1.8	1.8	6.2	6.1
Ascorbic acid added	99.4	94.2	94.8	1.3	1.3	3.9	3.9
Orange-lemon preparation	98.8	92.1	93.2	1.5	1.5	5.2	5.3
Fresh orange juice	93.9	88.0	93.7	1.3	1.4	4.6	4.9
Potassium							
Pre-experimental	136.0	106.4	78.2	19.4	14.3	10.2	7.5
Ascorbic acid added	133.5	108.5	81.3	16.8	12.6	8.2	6.1
Orange-lemon preparation	115.2	91.1	79.1	16.6	14.4	7.5	6.5
Fresh orange juice	120.3	89.7	74.6	14.5	12.0	16.1	13.4
Negative Minerals							
Phosphorus							
Pre-experimental	52.1	26.4	50.7	17.6	33.8	8.1	15.5
Ascorbic acid added	51.1	27.6	54.0	16.8	32.9	6.7	13.1
Orange-lemon preparation	53.2	27.4	51.5	19.3	36.3	6.5	12.2
Fresh orange juice	52.2	29.5	56.5	18.9	36.2	3.8	7.3
Chlorine							
Pre-experimental	165.1	147.9	89.6	2.9	1.8	14.3	8.7
Ascorbic acid added	161.5	150.4	93.1	2.5	1.6	8.6	5.3
Orange-lemon preparation	154.9	145.5	93.9	2.4	1.6	7.0	4.5
Fresh orange juice	147.8	140.5	95.1	2.5	1.7	4.8	3.2
Sulfur							
Pre-experimental	33.0	27.1	82.1	3.7	11.2	2.2	6.7
Ascorbic acid added	32.3	26.5	82.0	3.7	11.5	2.1	6.5
Orange-lemon preparation	32.1	28.4	88.5	3.5	10.9	0.2	0.6
Fresh orange juice	31.1	26.7	85.9	3.5	11.2	0.9	2.9

*The pre-experimental period includes 135 experimental days upon the four subjects who immediately afterward received a daily addition of 20 mg. ascorbic acid to their diets for a total (for the four) of 100 experimental days. Four children (two of whom participated in the investigation of ascorbic acid) received the orange-lemon preparation for 120 experimental days, and for a total of 60 experimental days an equivalent amount (50 c.c.) of fresh orange juice was substituted for the mixture.

weight basis. The mean intakes per kilogram of body weight of all the positive and negative mineral elements were lowered during the period of an added 20 mg. of ascorbic acid in the daily diet. Nevertheless, an appreciable increase (5.2 to 7.1 mg.) in average retention of calcium per kilogram of body weight occurred with the increased vitamin C intake, and magnesium storage was slightly greater (0.9 to 1.0 mg.). On the other hand, the mean retentions of sodium, potassium, phosphorus, and chlorine per unit weight decreased 2.3, 2.0, 1.4, and 5.7 mg. per day, respectively, and sulfur decreased from 2.2 to 2.1 mg. per day.

When 50 c.c. freshly prepared orange juice was substituted for the same quantity of orange-lemon preparation in the daily diets of four children, the daily intakes per kilogram of body weight were lowered for calcium (41.2 to 40.9 mg.), sodium (98.8 to 93.9 mg.), phosphorus (53.2 to 52.2 mg.), chlorine (154.9 to 147.8 mg.), and sulfur (32.1 to 31.1 mg.). During the fresh orange juice period, daily retentions per kilogram of body weight were increased from 5.0 to 6.3 mg. calcium, 1.4 to 2.7 mg. magnesium, and 0.2 to 0.9 mg. sulfur, results which corroborate those of Chaney and Blunt,[6] but are in contradiction to those of Daniels and Everson.[19] The daily potassium intake per kilogram was increased (115.2 to 120.3 mg.) by the fresh juice, but the per cent utilization doubled, the retentions increasing from 7.5 to 16.1 mg. per kilogram of body weight. The lowered intakes of sodium, phosphorus, and chlorine were accompanied by decreased daily retentions per kilogram of body weight, from 5.2 to 4.6 mg. sodium, 6.5 to 3.8 mg. phosphorus, 7.0 to 4.8 mg. of chlorine. It is demonstrated that the individual minerals behave differently in their metabolic activity. Although there was little difference on a unit weight basis between the average daily intakes of positive minerals (Table I) during ingestion of the orange-lemon preparation and fresh orange juice (10.3 to 10.2 meq., respectively), the average retention increased from 0.8 to 1.1 meq., raising the per cent utilization of the intakes from an average of 7.6 to 11.1. The daily intake of total negative minerals per kilogram of body weight (Table I) was reduced by the substitution of fresh orange juice (9.5 to 9.1 meq.) and the average retention was lowered (0.6 to 0.4), so that a decrease occurred in the per cent of intake utilized.

The metabolic adjustments taking place in response to the dietary changes are further shown in the excretion of mineral ions in urine and feces (Table II). With the additional ascorbic acid, calcium excretion dropped in both urine and feces to produce a greater average retention from the smaller intake. Excretion of magnesium was slightly higher in the urine, but in the feces it was lowered sufficiently to offset both the increased excretion in urine and the reduced intake, producing a higher retention. The decreased retentions per unit weight of sodium, potassium, phosphorus, and chlorine were produced

similarly; intakes were lowered, urine excretion was increased, and fecal excretion was decreased. The slightly reduced sulfur retention during the period of additional ascorbic acid apparently resulted from the lower intake per kilogram, for the variations in per cent intakes excreted in urine and feces were not significant, and the actual urine outgo was lessened.

Calcium excretion per kilogram of body weight dropped in both urine (3.6 to 3.2 mg.) and feces (32.6 to 31.4 mg.) under the influence of fresh orange juice; magnesium excretion was little changed in the urine (3.1 to 3.3 mg.), but was conserved by lowered output in feces; sodium excretion decreased in the urine (92.1 to 88.0 mg.), its major path of excretion, and in the feces (1.5 to 1.4 mg.); potassium elimination was also reduced in the urine (91.1 to 89.7 mg.) and feces (16.6 to 14.5 mg.). The elimination of phosphorus in urine during ingestion of the orange-lemon preparation (27.4 mg. per kilogram) was raised to 29.5 mg. per kilogram in the fresh orange juice determinations, changing from 51.5 to 56.5 per cent of intake and causing a smaller average retention since fecal excretion of phosphorus did not vary significantly. Chlorine metabolism conformed with that of the sodium, and the sulfur data varied only slightly. The means of the ion balances in the excreta (Table I) demonstrate that the substitution of fresh orange juice for the orange-lemon mixture resulted in a greater excretion of anions in the urine (0.70 to 0.78 meq.) and a reduction of cations in the feces (1.35 to 1.14 meq.) when considered on a unit weight basis. The laxation rate was not significantly changed during the two periods and does not account for the metabolic shifts that took place.

Viewing the various metabolic changes that occurred when 20 mg. of ascorbic acid was added to the daily diet and when 50 grams of freshly prepared orange juice was substituted for a like quantity of an orange-lemon preparation, it is evident that a different type of chemical growth occurred with each dietary regimen. Although there were differences in intensity of response among the highly standardized children, the trend of change was in the same direction for each dietary alteration and was consistent for the persons comprising each group. For these reasons consideration may be given to the group responses, demonstrating the metabolic influence of the orange-lemon preparation, with its lower, but more constant, vitamin C content, a supplement of 20 mg. ascorbic acid per child per day, and the replacement of the orange-lemon mixture with fresh orange juice.

Growth of both soft and hard tissues of each subject took place during all of the periods of observation; nitrogen and positive and negative minerals were retained. The addition of 20 mg. ascorbic acid to each child's mixed diet was accompanied by a reduction in mean retention of total minerals per kilogram of body weight, but

the average retentions of calcium and magnesium were increased and all subjects retained greater amounts of cations in relation to anions. Changes in nitrogen retentions were not conclusive. The trends of excretion and retention of the positive and negative minerals indicate that the additional vitamin C did permit the bodies of these well-nourished children to establish an increased rate of skeletal formation. This fact is further verified by the increase in the average calcium to phosphorus ratio from 0.64 to 1.06.

Substitution of an equivalent amount of fresh orange juice for the orange-lemon preparation improved the nitrogen and mineral metabolism of all the subjects, to a greater extent (on a unit weight basis), in general, than the addition of the ascorbic acid. Since the substitution of the fresh orange juice increased the total daily vitamin C intakes by an amount equivalent to 15 mg. ascorbic acid, its beneficial effect over and above that of the preparation, even with the added 20 mg. of ascorbic acid, hardly can be attributed to vitamin C alone. The increased intake of vitamin C with the substitution of fresh orange juice was no doubt responsible for the stimulation of hard tissue construction, but soft tissue synthesis was also accelerated, indicated by increased nitrogen retentions per kilogram for each child, a contrast to the response to purified vitamin C. The increase in soft tissue formation during the period of ingesting fresh orange juice is further shown in the increased ratio between nitrogen and phosphorus (1.54 to 6.84) in the retentions. The stimulated growth of hard tissues was indicated by augmented retentions of excess cations and by a doubled calcium-phosphorus ratio (0.77 to 1.66).

While the vitamin C contents of the diets ranged from 85 to 115 mg. per day, calculated upon the food group data given by Munsell,[27] the ascorbic acid intakes, calculated with the analytical values of Everson and Daniels,[18] averaged 5.3, 5.8, 7.0, and 7.8 mg. per kilogram of body weight per day for the orange-lemon preparation, fresh orange juice, pre-experimental period, and ascorbic acid period, respectively. Disregarding individuals, these authors found the "physiologic optimum" intake of ascorbic acid to be from 6.0 to 7.5 mg. per kilogram per day from the thirty-six five-day balances presented. The average ascorbic acid intakes per kilogram for their three experimental subjects during twelve balance periods for each child within four and one-half months were 5.6, 5.9, and 6.6 mg. per kilogram, and the retentions 2.8, 2.9, and 3.4 mg., respectively. The subjects of the present study were older than those studied by Everson and Daniels and were receiving an average amount of ascorbic acid comparable to that found by those authors to be the "physiologic optimum" during the pre-experimental period (7.0 mg. per kilogram daily). When 20 mg. of ascorbic acid was added to the daily diets, the average intake per kilogram was increased to 7.8 mg.; calcium

retention was increased, as was storage of cations in relation to anions, although the total amount of positive and negative minerals retained was reduced. The diets during administration of fresh orange juice provided an average of only 5.8 mg. of ascorbic acid per kilogram of body weight, yet the superior nutritive advantage of the fresh fruit was demonstrated, strengthening the belief that factors in addition to vitamin C were responsible.

COMMENT

The effectiveness of fresh orange juice over the orange-lemon preparation and the greater nutritive advantage of the fresh juice over a vitamin C supplement may reside in a number of factors. Diets with a potentially alkaline ash have been shown to improve the nitrogen retentions of children[30, 31] and dogs,[32] and vitamin C has been shown to be related to nitrogen retention.[18, 19, 21] Moreover, fresh orange juice may stimulate a greater gastric flow and, by means of its inherent buffer value, regulate the hydrogen ion concentration in the stomach in such a manner as to increase both digestion and absorption of calcium.[14, 15] It is significant that the calcium retention of children in this study was improved by the administration of additional ascorbic acid or by the inclusion of fresh orange juice, both producing a more efficient assimilation of the calcium contained in the diet, a fact which has recently been corroborated by Lanford[33] on rats. While additional vitamin C (in synthetic form or in fruit juice) may produce more efficient calcium utilization, the superior nutritive advantage of the fresh orange over the pure ascorbic acid strongly indicates that some other principle is present in the fresh juice and supports the same conclusions by other investigators.[34, 35] Nor may the attributes of the fresh fruit juice as a growth stimulant and nutritional stabilizer readily be credited to citric acid, for the orange-lemon juice preparation used contained juice partially dehydrated in vacuo and included an added 0.75 Gm. of citric acid in 50 Gm. of mixture.

The purposes of these studies were manifold: to find a citrus product which would be stable and provide a more constant, even though smaller, quantity of vitamin C than fresh oranges, which are known to vary widely in original composition and whose juice has been shown to be reduced in ascorbic acid content by as much as half from the processes of squeezing and straining in which exposure to air and contact with iron utensils (iron acting as a catalyst) permit oxidation; to ascertain the effect of an additional quantity of ascorbic acid in diets which were adequate according to accepted standards and were given to normal growing children; and to obtain an estimate of the relative nutritional values of ascorbic acid and fresh orange juice in the diets of healthy growing children. Since in none of the

studies were the mixed diets deficient in vitamin C, gross metabolic changes could not be expected from substitution of 50 c.c. of fresh juice for the same amount of the orange-lemon preparation, or even from the addition of 20 mg. ascorbic acid per day to each child's diet.

In a study of 427 infants during their first year of life,[25] an average intake of approximately 10 mg. of ascorbic acid per day was indicated as the minimum intake of vitamin C necessary to prevent minute signs of subclinical scurvy up to the age of 1 year. During the study of the infants, the vitamin C was supplied by a lemon juice powder which, because of its citric acid content, served to acidify the milk formula. To throw some light upon the possible value of citric acid in acidified formulas sometimes substituted for fresh fruit juice in pediatric practice, approximately 1.5 Gm. of citric acid were included in each 100 Gm. of the orange-lemon preparation. When the vitamin C contents of the diets were calculated, using the values presented by Everson and Daniels, the changes in average ascorbic acid intakes per kilogram of body weight were 0.5 mg. (5.3 to 5.8) for the substitution of fresh orange juice for the orange-lemon mixture, and 0.8 mg. (7.0 to 7.8) for the addition of the 20 mg. ascorbic acid in each child's daily diet. The levels of vitamin C intake from the fresh orange juice investigation are lower than those considered optimum by Everson and Daniels, and those of the ascorbic acid supplement investigation fall within the range they indicated as the "physiologic optimum" by their data. Yet the results of the present studies showed that the retention of nitrogen and minerals by the children was quite generally improved by substitution of fresh orange juice for the orange-lemon mixture, although the intake of vitamin C was raised only slightly and remained at a low level in comparison with the ascorbic acid investigation. When 20 mg. of the synthetic vitamin C (ascorbic acid) was added to diets which contained the same source (orange-lemon mixture) of vitamin C as the control diets for the fresh orange juice investigation and which already provided a higher average vitamin C intake, only calcium retention was significantly improved, and, although greater relative storage of cations to anions occurred, the total amount of positive and negative minerals stored was reduced.

The observations recorded in this paper emphasize the necessity of more extensive studies on the nutritional significance of fruit juices and comparable products in the diets of children before the vitamin C requirement for growth can be established in order to differentiate between nutrient principles in fresh orange juice and treated or prepared products, or even, prudently, to advise which is the best of these controlling food principles, especially in infancy when growth is most rapid and the number of different foods which may be included in the diet so limited.

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A SURVEY OF THE STATE OF NUTRITION WITH RESPECT TO VITAMIN C IN A SOUTHERN PEDIATRIC CLINIC

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INTRODUCTION

AMONG the patients attending the pediatric clinic at Vanderbilt Hospital, malnutrition due to economic factors or to ignorance or to both is so common that nutritional studies occupy a prominent place in our clinical investigations. From the general appearance of many of our patients and from their dietary histories, there can be no doubt that numerous dietary deficiencies exist. Yet only from scientific studies can we do more than speculate as to the nature of the nutritional lack or recommend the most practical and economical means of correcting the deficiencies. In earlier studies[1, 2] we reported the prevalence of mild nutritional hypoproteinemia with occasional manifestations of outspoken nutritional edema, and we have stressed the clinical complications which may arise from a poor state of protein nutrition. During the past year we have turned our attention to the state of nutrition with respect to vitamin C in the children of this locality. We see but little outspoken scurvy in our clinic, less, perhaps, than is reported in some other clinics dealing with patients of about the same economic standing. Is this because the usual local dietary, while often low in protein and deficient in calories, is nevertheless of a nature to furnish an adequate intake of vitamin C? Or are there many instances of moderate deficiency of vitamin C without clinical manifestations of scurvy, just as there were many instances of hypoproteinemia without edema?

The present paper is a report of our survey which is based upon the determination of ascorbic acid in the blood serum of over 500 children who came to our clinic. Included also is a brief discussion of the chemical properties of ascorbic acid and of the method for its determination. The practical difficulties encountered and the unavoidable limitations of accuracy which must be taken into account in evaluating a study of this kind are also considered.

CHEMICAL PROPERTIES OF ASCORBIC ACID AND THE PRINCIPLES INVOLVED IN ITS DETERMINATION

It is generally accepted that vitamin C is ascorbic acid.[3, 4, 5] Hence, the amount of ascorbic acid in foods determines their antiscorbutic efficiency, and similarly the amount of this acid in the body is an index to the state of nutrition

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with respect to vitamin C. In simple aqueous solution, ascorbic acid is an extremely unstable substance. It is readily oxidized merely on standing exposed to air at room temperature, first to dehydroascorbic acid and then promptly to further oxidation products. The oxidation proceeds more rapidly in neutral or alkaline solutions that in an acid medium and is greatly hastened by the catalytic effect of traces of copper.[6, 7, 8] These chemical properties impose the necessity for precautions in handling ascorbic acid and, at the same time, offer a convenient chemical means for its estimation. All manipulations involved in the extraction and preparation of ascorbic acid in foods and biologic material for quantitative determination must be carried out under conditions which minimize the possibility of loss through oxidation. Numerous procedures have been suggested to attain this end, but by far the most satisfactory results have been obtained with the use of metaphosphoric acid. This acid has been shown[9, 10, 11] to hinder markedly both the spontaneous oxidation of ascorbic acid and the catalytic effect of copper in hastening this oxidation. At the same time, metaphosphoric acid is an excellent reagent for the removal of protein from biologic solutions. Thus, through the use of metaphosphoric acid, one can obtain a protein-free solution containing the ascorbic acid extracted from the original material in a medium which will prevent loss through oxidation for a considerable period of time.

Advantage is taken usually of the ready oxidizability of ascorbic acid for its quantitative measurement. Of course, a substance which is readily oxidized is an active reducing agent. Solutions of the dye 2-6 dichloroindophenol are readily reduced to form a colorless solution by ascorbic acid in acid solution at room temperature.[12, 13] Solutions of this dye, the strength of which has been standardized against an ascorbic acid solution of known concentration, are most commonly used for the titration of ascorbic acid in unknown solutions. When all the ascorbic acid originally present is in the unoxidized form, reliable results are obtained by this titration, provided no interfering substances are present which are also capable of reducing the dye.[14] In properly prepared filtrates from blood (see details of method below), the amount of nonascorbic reducing substance is very small and constant, and no correction for it is necessary. On the other hand, when ascorbic acid is determined in extracts of complex material, such as foods, feces, etc., a considerable percentage of the total reducing power may be due to substances other than ascorbic acid. In such instances, further steps must be taken to distinguish between ascorbic acid and other reducing substances.[15, 16, 17] Since only blood was studied in this survey, further details in regard to the correction for interfering substances need not be considered here.

CHOICE OF MATERIAL TO BE STUDIED FOR SURVEY AND THE CRITERIA ADOPTED FOR INTERPRETATION OF RESULTS

What one really wants to know for an evaluation of the state of nutrition with respect to vitamin C is whether there is an adequate amount of ascorbic acid in the tissues, where it doubtless plays its indispensable role in normal biologic processes. Such information must obviously be gained by an indirect approach. Practically, we are limited to studies of the blood or urine. Experimental studies of various kinds have contributed information in regard to the correlation between the levels of ascorbic acid present in blood and urine and the probable status of vitamin C nutrition in the tissues. On an adequate or excessive intake of vitamin C, the concentration of ascorbic acid in the body tissues and fluids soon reaches a saturation level, and any excess is promptly

excreted in the urine. Several investigators[18-22] have independently arrived at essentially the same figure—1.0 to 1.5 mg. per 100 c.c.—as the concentration reached in the blood before there is a rapid excretion of any additional ascorbic acid taken in the diet. This level then appears to be the renal threshold for ascorbic acid, although, as is the case with many other so-called "threshold substances," there is some slight excretion below the threshold level.

In view of these findings, the assumption appears justified that, when the concentration of ascorbic acid in the blood is above 1.0 mg. per 100 c.c., or when considerable amounts (over 20 mg.) of ascorbic acid are excreted in a daily urine, the person in question is receiving an adequate intake of vitamin C and his tissues contain an adequate amount of ascorbic acid. There is more uncertainty in the interpretation of results which show a very low excretion in the urine and a concentration considerably below the threshold level in the blood. These figures in themselves only justify the conclusion that the intake of vitamin C is not as great as the person can take without rapid excretion in the urine. However, various experimental studies which have been reported indicate that a broader interpretation of simple data of this kind as a rough index of the degree of saturation in the tissues is justified. Following the administration of a rather large test dose of ascorbic acid (600 mg. to an adult) to a person whose tissues are well supplied with vitamin C, there is an abrupt temporary rise in ascorbic acid in the blood to above threshold level, and a considerable percentage of the dose is promptly excreted in the urine. On the other hand, in a person whose tissues are markedly deficient in vitamin C, the same test dose causes a much less marked rise in the blood and little or no excretion in the urine. Presumably, the unaccounted-for ascorbic acid is largely taken up by the tissues. A correlation of the results of such tests with the initial levels of ascorbic acid in the blood before the test dose had been given has been worked out by Goldsmith and Ellinger[22] on twenty-five patients with widely varying initial levels of ascorbic acid. Consistently they found that persons with fasting levels of 0.7 mg. or more per 100 c.c. showed a prompt rise in the level of ascorbic acid in the blood and an excretion of a considerable percentage of the dose in the urine. In other words, these persons gave evidence of being fairly well saturated with ascorbic acid. In patients with initial levels significantly below 0.7 mg. per 100 c.c. of blood, there was, in nearly every instance, evidence of some degree of unsaturation in that very little of the dose was excreted and there was only a moderate increase in the level in the blood. In the presence of grossly low initial values in the blood, in the order of 0.1 mg. per 100 c.c., the test dose caused but little rise in the blood and no increase in the urine, indicating that the tissues were markedly unsaturated and were picking up a large portion of the ingested vitamin.

Our survey was planned, and the criteria for the interpretation of the results obtained were adopted on the basis of the information just discussed. From patients of pediatric age blood samples can be obtained much more easily than twenty-four-hour samples of urine. Hence, we decided to study blood. Serum, rather than whole blood or plasma, was used largely as a matter of technical convenience in the clinic. Blood is drawn routinely for Wassermann tests on all new patients, and by simply increasing the size of the sample taken, enough serum was obtained for both the determination of vitamin C and for the serologic test. We have assumed that levels of 0.7 mg. or more of ascorbic acid per 100 c.c. of serum indicate a reasonably satisfactory state of nutrition with respect to vitamin C. Lower values from 0.3 to 0.7 mg. per 100 c.c. have been interpreted as indicative of a moderate degree of deficiency. Values lower than 0.3 mg. per 100 c.c. are regarded as evidence of a serious deficiency of vitamin C.

METHOD FOR DETERMINATION OF ASCORBIC ACID IN SERUM

The method used for the determination of ascorbic acid was essentially the macromethod described by Farmer and Abt.[11] The blood was drawn from patients as they came to our clinic, usually three or four hours after their morning meal. The serum was promptly removed from the clotted blood by centrifugalization. To one volume of serum two volumes of distilled water and two volumes of 5 per cent metaphosphoric acid solution were immediately added. After vigorous shaking, the mixture was allowed to stand thirty minutes or longer. In order to obtain as large a yield of filtrate as possible, the bulk of precipitated protein was usually removed by centrifugalization and the supernatant fluid filtered through a small filter. In this manner, sufficient filtrate for duplicate determinations can be obtained easily from 2 c.c. of serum. Aliquot portions of 2 c.c. of the protein-free filtrate were titrated against a white background with a 1:50 dilution of the stock solution (see below) of 2-6 dichloroindophenol added from a microburette. The first purplish pink color which persisted for as long as thirty seconds was taken as an end point. A correction for the titration blank was made in each case. This value was obtained by determining the amount of diluted dye required to produce the same end point when added to 2 c.c. of acidulated distilled water.

The stock solution of the dye contained approximately 75 mg. of 2-6 dichloroindophenol dissolved in hot distilled water, filtered, and finally made to a volume of 100 c.c. in a volumetric flask. The ascorbic acid factor for this solution of dye was determined by titrating a freshly prepared ascorbic acid solution of known strength. Usually, 1 c.c. of the stock solution was found to be equivalent to between 0.3 and 0.4 mg. of ascorbic acid. For the titration of filtrates obtained from serum, a 1:50 dilution of this stock solution was found most suitable. The stock solution has been found to remain unchanged for a week or more if kept in a cool dark place. Fresh 1:50 dilutions were prepared for use each day.

EXPERIMENTAL RESULTS

When our survey was brought to a close we had obtained data on 540 children. Seven of these results were discarded because the children were practically in a state of starvation due to some mechanical interference with the ingestion of food, and hence, were not desirable

subjects to include in a nutritional survey. The remaining 533 were divided into the following three main subdivisions: (a) 380 children with no serious complaint or disease; (b) 105 sick children without diarrhea; and (c) 48 sick children with diarrhea as the chief complaint. The data obtained in these groups will be discussed under separate headings.

Children With No Serious Disease.—In this group are included well children who visited our clinic for routine examination or immunization, treated syphilities, children with inactive tuberculosis, and those with minor complaints which one would not expect to interfere in any way with the state of nutrition. None of them had fever. For the sake of brevity in subsequent discussion, this group will be referred to as "normal." In each case an attempt was made to get a dietary history, but in many instances the information obtained was fragmentary and inaccurate.

Further subdivisions appeared desirable as we proceeded in the analysis of the data in the "normal" group. In this locality, fresh vegetables become plentiful in gardens and much cheaper in the markets by about the first of June. This makes an adequate intake of vitamin C much more readily available during the summer than the winter and early months of spring. We, therefore, subdivided our results on the basis of the date on which the study was made. One group included observations made from February 1 to June 1, and the other group, those made from June 1 to October 1. Since one would expect that the ready availability of fresh fruit and vegetables would bring about much less change in the diet of very young children than it would in older persons, further subdivisions were made on the basis of age.

According to this scheme, our 380 observations on normal children were distributed as follows:

39 on children under 3 years from Feb. 1 to June 1
47 on children under 3 years from June 1 to Oct. 1
43 on children from 3 to 8 years from Feb. 1 to June 1
77 on children from 3 to 8 years from June 1 to Oct. 1
72 on children from 8 to 15 years from Feb. 1 to June 1
102 on children from 8 to 15 years from June 1 to Oct. 1

A summary of the ascorbic acid concentration found in the blood sera in these various subgroups is presented in Table I.

Even a casual observation of the data obtained answers one question raised in our introductory discussion. There is considerable undernutrition with respect to vitamin C among the clinic group in this locality. During the months in which fresh fruit and vegetables are scarce, about 60 per cent of the children in all age groups had levels of ascorbic acid in the serum below the generally accepted

TABLE I

DISTRIBUTION OF ASCORBIC ACID VALUES IN "NORMAL" CHILDREN ACCORDING TO AGE AND SEASON

AGE GROUP (YR.)	DATE GROUP	TOTAL NUMBER OBSERVATIONS	VALUES ABOVE 0.7 MG. PER 100 C.C.		VALUES BELOW 0.7 MG. PER 100 C.C.		VALUES BELOW 0.3 MG. PER 100 C.C.	
			NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Under 3	Feb. 1 to June 1	39	14	36.0	25	64.0	17	43.5
Under 3	June 1 to Oct. 1	47	19	40.0	28	60.0	14	30.0
3-8	Feb. 1 to June 1	43	16	37.2	27	62.8	16	37.2
3-8	June 1 to Oct. 1	77	40	52.0	37	48.0	7	9.1
8-15	Feb. 1 to June 1	72	30	41.6	42	58.4	22	30.5
8-15	June 1 to Oct. 1	102	65	63.7	37	36.3	12	11.7

satisfactory level of 0.7 mg. per 100 c.c. About 30 or 40 per cent had levels below 0.3 mg. per 100 c.c., which are indicative of a serious lack of vitamin C in the dietary. During the summer months when fruit and vegetables are plentiful and cheap, there is an obvious shift in the distribution of ascorbic acid levels in the blood of older children. A considerably larger percentage reach a satisfactory level, while only about 10 per cent still give evidence of gross undernutrition with respect to vitamin C. The seasonal variation, however, is very slight in the group under 3 years of age, presumably because their dietary is changed much less.

In order to demonstrate more conclusively that the observed seasonal variation in ascorbic acid levels in the serum was merely an expression of dietary changes in the group as a whole, we carried out more intensive studies on twenty-five persons in the "normal" group. The ascorbic acid concentration of the serum of these children was determined in the early months of the year and then again in midsummer. Besides this, the homes were visited, and the nature of the diet which was available, the eating habits of the child, etc., were all carefully investigated. With an accurate dietary history available, there was a close correlation between the levels of ascorbic acid found in the serum and the dietary intake regardless of the time of the year. Children whose diet had remained unchanged showed about the same levels in the serum on the two observations. In other instances, when the family had a garden and a liberal supply of vegetables in contrast to a lack during the winter, there was a marked rise in the ascorbic acid content of the serum during the summer. In a few families, economic reverses had made the summer diet less complete than the winter one had been, and in these instances, a decrease rather than an increase was found in the midsummer determinations of ascorbic acid

as compared to the earlier observations. Space does not permit the presentation of the detailed information on all these twenty-five patients, but six typical cases are collected in Table II in order to illustrate the points we have just brought out.

TABLE II

CORRELATION OF DIETARY HISTORY WITH SEASONAL VARIATIONS IN ASCORBIC ACID LEVEL OF SERUM

NO.	AGE (YR.)	MG. ASCORBIC ACID IN 100 C.C. SERUM		DIETARY HISTORY
		BEFORE JUNE 1	JULY-AUGUST	
1	1	0.34	0.26	Condensed milk formula. No orange juice. Very little supplementary food. No change in diet between the two observations.
2	6	0.33	0.31	Family in poor circumstances. Ate mostly dried beans, corn bread, and fat meat. Almost no vegetables. Diet unchanged between observations.
3	4	0.76	0.96	Has a good diet with fresh fruits and vegetables daily, even in the winter. Diet not much different in summer, except vegetables are more plentiful.
4	8	0.09	1.01	During the winter had beans, potatoes, bread and butter, with no vegetables. In the summer she had this diet plus plenty of vegetables from the garden.
5	4	0.36	1.11	Lived in country. In the winter had plenty to eat, but no fruit or vegetables. In the summer there was a liberal supply of vegetables from garden.
6	3	0.78	0.31	During the winter the diet was fairly satisfactory. In the summer the father lost his job, and the family dietary was very much reduced. Had no garden and could buy no fruit or vegetables.

SICK CHILDREN WITHOUT DIARRHEA

Most of the patients in this group were hospitalized, and practically all had fever of 100° F. or more. The diseases represented were distributed roughly as follows:

Diseases of the respiratory tract, including tuberculosis, 40
Some phase of the rheumatic syndrome, 15
Diseases of the urinary tract, 13
Localized infections, 22
Miscellaneous, 15

These observations were made throughout the period from February to October, and the entire range of pediatric ages was included. Since there were many more instances of vitamin C deficiency in "normal" children under 3 years of age than in the older groups, it seemed desirable to subdivide the "sick" group on the basis of age before a comparison was made of the data in the "sick" and "normal" groups.

There were forty-one "sick" children under 3 years of age, and sixty-four between 3 and 15 years. For ease in comparison, the data in "sick" and "well" groups are summarized in Table III.

TABLE III

COMPARISON OF ASCORBIC ACID VALUES IN "SICK" AND "NORMAL" CHILDREN

GROUP	TOTAL NUMBER OF OBSERVATIONS	VALUES ABOVE 0.7 MG. PER 100 C.C.		VALUES BELOW 0.7 MG. PER 100 C.C.		VALUES BELOW 0.3 MG. PER 100 C.C.	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
"Normal" children under 3 years in all seasons	86	33	38.4	53	61.6	31	36.0
"Sick" children under 3 years in all seasons	41	5	12.2	37	87.8	25	62.5
"Normal" children of 3-15 years in all seasons	294	151	51.4	143	48.6	57	19.4
"Sick" children of 3-15 years in all seasons	64	22	34.4	42	65.6	20	31.2

Many more of the "sick" than the "normal" children have frankly low levels of ascorbic acid in the serum. Again, the highest percentage of low values is found in the younger age group. It is difficult to know how much of the decrease from normal in a sick child should be ascribed merely to loss of appetite and limitation of diet and how much to increased needs imposed by the disease itself. From our small numbers of observation there was no evidence that any particular type of disease influenced the state of nutrition with respect to vitamin C to a greater or less extent than others. On the basis of the rough classification of diseases given above the distribution of ascorbic acid values found in each subgroup of diseases closely followed that of the "sick" group as a whole. Children with a previous history of an only fairly satisfactory or deficient diet all had low values of ascorbic acid in the serum when they were sick. Some were low despite what appeared to be a liberal intake of vitamin C as judged by the requirements of normal children.

Our results showing a general trend to lower concentrations of ascorbic acid in the serum in the presence of disease are in accord with the reports of numerous other investigators.[23, 24, 25] Whatever factors may be responsible for this tendency, it is apparent that special efforts to continue or to increase the intake of vitamin C are necessary if normal concentrations of ascorbic acid are to be maintained in sick children. Such measures appear to be an essential part of adequate supportive

treatment in any disease if ascorbic acid plays the indispensable role it is believed to play in normal biologic processes.

Sick Children With Diarrhea as the Chief Complaint.—Since the ability both to take and to absorb food is more radically interfered with in sick children whose primary disturbance is in the gastrointestinal tract, we have collected our data on patients with diarrhea as a chief complaint in a separate group. There were forty-eight persons, including those with bacillary dysentery and those with severe nonspecific diarrheas. All except three were hospitalized, and all except four were under 3 years of age. The results obtained are summarized in Table IV. One is impressed with the large percentage of extremely low values

TABLE IV

DISTRIBUTION OF ASCORBIC ACID VALUES IN SERUM FOUND IN FORTY-EIGHT CHILDREN WITH DIARRHEA

NUMBER OF CHILDREN	PERCENTAGE	ASCORBIC ACID VALUE IN SERUM
8	16.5	Over 0.7 mg. per 100 c.c.
40	83.5	Under 0.7 mg. per 100 c.c.
31	61.5	Under 0.3 mg. per 100 c.c.
22	45.9	Under 0.2 mg. per 100 c.c.
13	27.1	Under 0.1 mg. per 100 c.c.

indicating a serious deficiency of vitamin C in the majority of patients with diarrhea. Actually, however, the percentage of values under 0.3 mg. of ascorbic acid per 100 c.c. is essentially the same in sick children under 3 years of age, both with and without diarrhea. Failure to take food and poor absorption probably are more important factors in causing the low levels in the children with diarrhea. Chinn and Farmer[17] have recently reported an increase in the excretion of ascorbic acid in the stools in patients with enteritis. Work along this line is being undertaken here, both before and after the administration of large doses of ascorbic acid by mouth. At present we can only report that large daily oral doses, from 10 to 20 mg. per kilogram, of ascorbic acid for a period of one week or longer have frequently been found inadequate to restore or to maintain a satisfactory level of ascorbic acid in the serum of young children with severe diarrhea. The same doses usually suffice rather promptly to restore the level to values well above 1.0 mg. per 100 c.c. in normal children of similar age. Whatever the cause of the deficiency, it is again apparent that young sick children, either with or without diarrhea, are frequently subjected to a serious lack of vitamin C unless strenuous measures are taken to supply the extra amount required.

GENERAL COMMENT

When all is said and done, we are still left without any adequate explanation as to why we see so little clinical evidence of scurvy in a group of children among whom malnutrition and gross inadequacies of diet are so general. To be sure, our most frequent finding was an

ascorbic acid level in the serum indicative of a moderately low intake of vitamin C, rather than a necessarily serious deficiency. There were, however, large numbers of children with ascorbic acid levels so low as almost surely to be associated with a rather marked degree of deficiency of vitamin C in the tissues. Even when a careful study of roentgenograms was made, together with a search for any other clinical evidence of scurvy in children whose levels of ascorbic acid were known to run persistently below 0.2 mg. per 100 c.c. of serum, we failed in most instances to find characteristic evidence of the deficiency. It would be exceedingly difficult to estimate how much of the vague symptom complex of lack of energy, lack of appetite, mental apathy, and generally retarded development so frequently seen in these children could be ascribed with justification to deficiency in vitamin C. Possibly the low calorie intake of many of our patients, with the resultant slow growth and development and tendency to inactivity, may influence the level of deficiency which must be reached before the generally recognized symptoms of scurvy appear. In historic accounts of scurvy among sailors and explorers, mention is often made of the fact that the most serious manifestations of deficiency were seen in persons with tasks involving greater exposure and activity. It is possible also that a combination of deficiencies such as many of these children must have may lead to a suppression of so many bodily processes that symptoms fail to appear with a degree of deficiency of ascorbic acid which, by itself, would produce evidence of scurvy. An analogy in support of this suggestion comes from studies of vitamin B.[26, 27] It has been observed that, in a person deficient in numerous fractions of the B complex, the administration of one fraction may bring out symptoms of acute lack of some other fraction which had been latent as long as the more complete lack of the whole complex persisted. Possibly we would see more outspoken scurvy if the local dietary of our clinic group was improved in other respects, but with no increase in vitamin C. However, a great deal more will have to be known about the interrelations of the actions of various food factors before any weight can be given to suggestions of this kind.

SUMMARY AND CONCLUSIONS

A survey of the ascorbic acid levels in the blood serum of over 500 clinic patients of pediatric age living in the vicinity of Nashville, Tenn., has been made.

Evidence was cited which appears to justify the following criteria for the evaluation of results: Values of 0.7 mg. and over per 100 c.c. of serum are indicative of a satisfactory state of nutrition with respect to vitamin C. Values of from 0.3 to 0.7 mg. per 100 c.c. indicate a restricted intake, but may or may not be associated with any serious undersaturation of the tissues with ascorbic acid. Values under 0.3 mg. per 100 c.c. indicate a serious deficiency of vitamin C.

On the basis of these assumptions, our results indicate that approximately 50 per cent of the children without significant diseases are in an unsatisfactory state of nutrition with respect to vitamin C. A greater percentage of "normal" children under 3 years of age have levels of ascorbic acid under 0.3 mg. per 100 c.c. than in the older groups. There is considerable seasonal variation. During the summer months when vegetables and fruit are cheap and plentiful, a considerably larger percentage have serum ascorbic acid values above 0.7 mg. per 100 c.c. than do during the winter and early spring. In very young children whose dietaries vary less throughout the year, the seasonal difference is less apparent. Of the entire group of "normal" children, approximately 35 per cent during the winter, and 20 per cent during the summer, have ascorbic acid values indicative of serious undernutrition with respect to vitamin C.

A much larger percentage of sick children, both with and without diarrhea, show low values of ascorbic acid in serum. Again, in this group, the greater percentage of very low values is found in children under 3 years of age. In many instances it is difficult to know how great a role failure to eat and limitation of diet may play in bringing about the deficiency in sick children. These factors probably are of considerable importance in gastrointestinal disturbances. Children with diarrhea have been found to require very large oral doses of ascorbic acid to maintain satisfactory levels in the blood.

Whatever the mechanism of the deficiency may be, our results indicate the necessity for taking measures to provide extra vitamin C for sick children in order to prevent a serious lack of this essential food factor during their disease.

The question still remains unanswered as to why clinical evidence of scurvy is so seldom seen among the rather large group which is apparently grossly deficient in vitamin C. The suggestion is made that diets which are simultaneously deficient in calories and several essential food factors may suppress the typical manifestations of deficiency, despite low levels of ascorbic acid which, in otherwise adequately nourished persons, would cause outspoken scurvy.

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SOME RESPONSES OF THE CHILD TO EXERCISE

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THE importance of some of the fundamental homeostatic factors such as cardiovascular adjustment and acid-base equilibrium in the problem of fatigue is recognized, and likewise, the extraordinary capacity which the organism has to make almost immediate adjustment in the face of the least derangement of these functions. To attempt to capture phases of this rapid and subtle adjustment or to demonstrate and measure even minute or minor alterations from the normal, which might conceivably occur when even early evidences of fatigue set in, was the object of this study.

The present report represents the results of a study of twelve children ranging in age from 11 to 13 years. The study has included determinations of the changes in heart rate and systolic and diastolic pressures resulting from both moderate and maximal work on the bicycle ergometer, determinations of the changes in many of the components of the blood under the two conditions of work, and an attempt to determine whether or not any of these findings could be related to the nutritive status or the physical capacity of the child.

Whereas the effects of muscular exercise upon the composition of the blood have been studied intensively in the dog and the adult man, similar studies on the child have received little attention. Schlutz and Blish[1] have shown that after fifteen minutes of exercise, the content of fixed acid in the child's blood is increased, but if exercise is continued longer, the concentration of fixed acid tends to fall again. The rise in fixed acid with exercise is also markedly reduced by training. In comparing the asthenic with the normal child, they found that, although averages of the entire series show little difference in response to exercise, the children showing spectacular rises in the level of fixed acid are definitely asthenic and that the asthenic child shows less marked response to training than the normal child.

Robinson[2] has recently reported a comprehensive study of physical fitness in relation to age, which has included children of all ages beginning as young as 5.7 years. While most of the study has been devoted to changes in heart rate, oxygen intake and lung ventilation during exercise, measurements of the various subdivisions of the lung volume, and the composition of arterial blood during rest, it has included the

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effects of exercise upon the blood sugar and lactic acid. When walking, children and young men show the same slight rise in blood lactic acid, but when maximal work is being performed the large rise in lactic acid is less marked in the younger children and becomes greater with increasing age until it reaches a maximum in men of from 30 to 40 years. Walking usually produces a slight rise in blood sugar in children as well as in men of all ages, but severe exercise produces a hyperglycemia in all but the youngest boys and the oldest men.

EXPERIMENTAL PROCEDURE

Experiments were carried out early in the morning, the children having fasted since the previous evening meal. Initial pulse rate and systolic and diastolic pressures were determined, and an 8 c.c. venous blood sample was drawn while the child rested in position on the bicycle ergometer. Some stasis was required in order to secure the blood sample. Immediately after exercise, pulse rate and systolic and diastolic pressures were determined in fifteen-second consecutive intervals for two minutes. The drawing of another 8 c.c. venous blood sample followed immediately after and was usually completed five minutes after exercise had ceased.

One cubic centimeter of each blood sample was introduced under oil into a small receptacle containing potassium oxalate. This sample was used for the determination of blood sugar, hemoglobin, cell volume, pH, and blood CO_2. The remainder of the sample was introduced under oil into a 15 c.c. centrifuge tube, centrifuged, and the serum removed under oil. The serum was analyzed for lactate, phosphate, total nitrogen, chloride, and sodium.

Micromethods of analysis were used. Hemoglobin was determined according to Evelyn,[3] in the photoelectric colorimeter. The microtechnique of Shock and Hastings,[4] made possible the determination of cell volume, pH, and total CO_2 on a single 0.1 c.c. blood sample. Plasma CO_2 was calculated from pH and total CO_2, using the factors of Van Slyke and Sendroy.[5] Blood sugar was determined by the micromethod of Folin.[6] Serum lactate was determined by adapting the method of Avery and Hastings[7] to 0.2 c.c. samples. Inorganic phosphate was determined on a 0.2 c.c. sample by adapting the Fiske-Subbarow method,[8] to use with the Evelyn photoelectric colorimeter. Total nitrogen was determined on 0.1 c.c. samples by the micro-Kjeldahl method of Pregl,[9] chloride on 0.1 c.c. samples using the titrimetric silver iodate—thiosulfate method of Sendroy,[10] and sodium on 0.2 c.c. samples by the micromethod of Hoffman and Osgood.[11]

Each child came in once a week for five weeks to participate in the experiment. For the first three weeks exercise on the bicycle ergometer[12] was moderate and fixed in amount. Each child was asked to ride for fifteen minutes at such a speed as to generate a terminal voltage of 7. This required about fifty revolutions of the pedals per minute and represented the performance of 1,750 foot pounds of work per minute. Such work was accomplished with comparative ease by all but one of the sub-

jects. This child (D. A.) succeeded in maintaining the desired rate of work in one experiment when he was asked to keep the voltmeter recording needle at 8.

The experiments for the last two weeks were designed to test the physical capacity of the child. After riding five minutes at the moderate speed, the child was asked to ride as fast as possible for one minute and to try to make the voltmeter needle move out to the end of the scale (15 volts). An interest in trying to make the voltmeter needle move off the scale stimulated most of the children to maximal performance. Three of the children succeeded, although their maximum speed lasted about fifteen seconds. The voltmeter reading was recorded automatically by a pen tracing. A comparative estimate of the accomplishments of the different subjects was secured by studying the superimposed tracings. Of the twelve children, three (R. W., F. C., and L. S.) were rated superior; three (W. P., J. G., and R. B.), good; four (M. G., P. P., J. Ba., and R. H.), fair; and two (J. Bo. and D. A.), poor.

NUTRITIVE STATUS OF THE SUBJECTS

The data showing the nutritive status of each of the subjects is given in Table I. The subjects were chosen to represent underweight, normal, and overweight types. Two (M. G. and J. G.) were girls, and the rest, boys. Four (R. W., R. B., R. H., and J. Ba.) were negroes. M. G. and J. G. were sisters, and W. P. and P. P., brothers.

TABLE I

MEASUREMENT OF THE NUTRITIVE STATUS OF THE SUBJECTS

SUBJECT	AGE (YEARS)	WEIGHT (KG.)	HEIGHT (CM.)	BALDWIN-WOOD RATING	MC CLOY RATING			CREATININE COEFFICIENT (MG./KG.)	MUSCLE (CREATININE) INDEX
					INDEX OF BUILD	INDEX OF WEIGHT	INDEX OF FAT		
J. G.	12 6/12	28.0	141.6	0.809	0.86	0.93	0.56	20.2	0.92
W. P.	13 11/12	35.9	154.4	0.835	0.91	0.92	0.68	23.2	1.04
R. H.	12 6/12	32.5	149.6	0.850	0.85	0.99	0.73	25.3	1.22
D. A.	11 5/12	27.2	138.9	0.864	0.90	0.96	0.69	19.7	1.04
J. Ba.	11 8/12	30.3	143.3	0.881	0.89	1.00	0.71	24.8	1.20
M. G.	11 3/12	32.7	145.1	0.898	0.92	0.98	0.67	19.0	0.90
R. B.	11 6/12	33.3	144.3	0.949	0.92	1.03	0.87	27.0	1.35
L. S.	11 3/12	39.3	149.8	0.971	1.00	1.03	0.82	25.8	1.30
P. P.	11 4/12	42.4	145.9	1.171	1.07	1.09	1.13	21.1	1.12
R. W.	13 9/12	64.7	164.3	1.281	1.14	1.13	1.09	19.4	1.08
J. Bo.	12 2/12	52.6	149.5	1.378	1.18	1.15	1.71	9.6	0.54
F. C.	12 11/12	63.3	158.2	1.404	1.14	1.23	1.61	14.9	0.90

According to the Baldwin-Wood[13] rating based on height, weight, age, and sex, six of the subjects would be classed as underweight and four overweight (allowing ± 10 per cent as the normal range). According to the McCloy[14] rating which takes into account other skeletal measurements, chest circumference, hip width, and knee width, as well as height,

only two of the subjects would be considered underweight, although eight were below the average in respect to body fat. The majority of the subjects were of the narrow asthenic type.

The creatinine coefficients were determined to supplement the anthropometric measurements. The children were hospitalized long enough to collect an accurate twenty-four-hour urine specimen. Meat was withheld from the diet for twenty-four hours preceding and during the collection of the specimen. The creatinine of the urine was determined by Folin's method,[15] and the creatinine coefficient was calculated in milligrams per kilogram body weight. Except for the two definitely overweight children, the values all fell within the range found by Talbot[16] for normal children.

It was felt that the creatinine data could be used to better advantage if the twenty-four-hour creatinine excretion were considered in relation to the skeletal build of the child. The "normal weight" as developed by McCloy gives the average weight of children of the same skeletal build. The "normal" twenty-four-hour excretion of creatinine of a child of given skeletal build might then be determined by multiplying the "normal weight" by 20.5, the average creatinine excretion per kilogram of body weight found by Talbot. Following this reasoning, a creatinine index was found for each child by dividing the actual creatinine excretion by the "normal" excretion. The indices so calculated are independent of the fat factor and would seem to be useful as a measure of the relative amount of muscle in the different subjects. It is interesting to note that the creatinine indices account very well in most instances for the discrepancy between the weight and the fat index of each child. The results indicate a muscle content definitely lower than the normal for the two obese boys and the two girls, and definitely higher than the normal for the three thin negro boys and one muscular, but thin, white boy.

OBSERVATIONS

Tables II and III give the average value, the range in value, the standard deviation, and the coefficient of variation for each factor measured before exercise and after both moderate and maximal work. The means represent the average of two or three experiments on each of the twelve children.

The resting values of the two sets agree very well. Except for serum lactate, the greatest individual variations in resting values occur in the cardiovascular measurements, diastolic and systolic pressures, and pulse rate. Serum pH, chloride, sodium, and the total determined anions show a coefficient of variation of not more than 1.3 per cent. After moderate work the coefficient of variation is increased significantly in the cases of diastolic pressure and serum bicarbonate and lactate. After maximal work serum lactate shows less individual variation than after

TABLE II

EFFECTS OF MODERATE WORK

FACTOR MEASURED	AT REST				AFTER MODERATE WORK			
	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Pulse rate, beats per min.	86	73-112	± 9.0	10.6	143	115-168	± 14.8	10.4
Systolic pressure, mm. Hg	111	95-131	± 9.9	8.8	141	121-160	± 13.5	9.7
Diastolic pressure, mm. Hg	76	59-89	± 8.6	11.3	65	42-89	± 14.6	22.5
Pulse pressure, mm. Hg	36	29-52	± 5.9	16.4	76	50-96	± 12.7	16.9
Hemoglobin, Gm./100 c.c.	13.5	12.3-14.6	± 0.7	5.4	14.0	12.8-15.4	± 0.7	5.3
Red cell volume, per cent	41.9	39.6-46.6	± 3.4	8.2	43.2	41.2-46.5	± 1.9	4.3
Serum protein, Gm./1.	72.9	67.3-79.9	± 3.7	5.1	75.9	68.0-80.2	± 3.6	4.7
Blood sugar, mM/1.	5.13	4.24-5.76	± 0.41	7.9	5.36	4.59-6.49	± 0.44	8.3
Serum phosphate, meq./1.	2.66	2.36-2.85	± 0.15	5.6	2.76	2.48-2.95	± 0.15	5.5
Serum pH	7.36	7.29-7.40	± 0.04	0.5	7.36	7.28-7.41	± 0.05	0.6
Serum bicarbonate, meq./1.	25.0	23.3-26.0	± 1.0	4.1	20.9	17.4-24.4	± 2.4	11.3
Serum bicarbonate, at initial pH. meq./1.	25.0	23.3-26.0	± 1.0	4.1	20.8	17.3-25.3	± 2.6	12.7
Serum lactate, meq./1.	2.19	1.47-3.27	± 0.50	22.8	5.64	2.71-8.62	± 1.94	34.5
Serum CO_2 tension, mm. Hg	45.7	39.7-52.3	± 3.4	7.4	38.5	32.0-43.9	± 3.8	9.9
Serum chloride, meq./1.	106.4	104.4-108.6	± 1.1	1.1	107.1	105.1-108.6	± 1.1	1.0
Serum Σ anions, meq./1.	153.8	150.2-155.8	± 1.6	1.0	154 8	151.2-156.3	± 1.6	1.0
Serum sodium, meq./1.	137.8	135.5-140.9	± 1.5	1.1	138.1	136.0-140.1	± 1.2	0.9

TABLE III

EFFECTS OF MAXIMAL WORK

FACTOR MEASURED	AT REST				AFTER MAXIMAL WORK			
	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Pulse rate, beats per min.	85	70-102	± 8.8	10.4	149	124-172	± 10.6	7.1
Systolic pressure, mm. Hg	114	96-133	± 10.7	9.4	148	120-189	± 21.2	14.3
Diastolic pressure, mm. Hg	75	53-90	± 10.4	13.9	69	46-92	± 15.6	22.6
Pulse pressure, mm. Hg	39	31-48	± 5.5	14.1	79	62-114	± 10.5	13.3
Hemoglobin, Gm./100 c.c.	13.5	12.4-14.4	± 0.7	5.0	14.3	13.1-15.3	± 0.6	4.4
Red cell volume, per cent	41.4	38.8-46.3	± 2.1	5.2	44.0	42.4-46.3	± 1.4	3.2
Serum protein, Gm./1.	72.7	68.0-80.2	± 3.8	5.2	76.9	71.4-84.4	± 3.9	5.1
Blood sugar, mM/1.	5.08	4.26-5.82	± 0.44	8.7	5.30	4.56-6.62	± 0.57	10.4
Serum phosphate, meq./1.	2.70	2.56-2.91	± 0.11	4.1	2.83	2.65-3.01	± 0.07	2.5
Serum pH	7.37	7.33-7.42	± 0.03	0.4	7.25	7.15-7.36	± 0.07	0.9
Serum bicarbonate, meq./1.	24.7	22.0-27.8	± 1.7	7.0	18.5	15.8-22.2	± 1.8	9.9
Serum bicarbonate, at initial pH, meq./1.	24.7	22.0-27.8	± 1.7	7.0	15.4	11.2-21.8	± 2.9	18.8
Serum lactate, meq./1.	2.22	1.47-3.33	± 0.60	26.5	10.01	5.80-15.62	± 2.55	25.5
Serum CO_2 tension, mm. Hg	44.7	35.1-54.2	± 5.6	12.5	42.6	29.5-53.0	± 6.9	16.2
Serum chloride, meq./1.	106.9	104.6-108.7	± 1.3	1.3	107.0	104.7-109.7	± 1.6	1.5
Serum Σ anions, meq./1.	154.4	151.6-156.7	± 1.7	1.1	156.2	153.3-158.9	± 1.9	1.2
Serum sodium, meq./1.	138.1	135.0-141.3	± 1.7	1.3	139.1	136.1-141.5	± 1.6	1.2

moderate work, while systolic, as well as diastolic, pressure and serum sugar and CO_2 tension show a greater coefficient of variation than before.

The changes brought about in each measured factor by exercise of both a moderate and a maximal character are summarized in Table IV. This table gives the changes in each factor as measured by the average of all the experiments and the standard deviation from this average as calculated by the formula, $\sqrt{\frac{\Sigma(\triangle - \overline{\triangle})^2}{N-1}}$, on the somewhat doubtful assumption that the variations follow the law of normal distribution. All of the changes due to exercise have been tested for significance by calculation of the "T" factor for paired data. It is interesting to note that, with the exception of serum pH and sodium during moderate work, and diastolic pressure, blood sugar, serum chloride, and CO_2 tension during maximal work, all of the factors measured showed significant changes as the result of exercise.

Since we were especially interested in detecting any possible relation of each factor to the nutritive or physical status of the child, we have emphasized the variations by including in the table those children whose deviations from the average of the group exceed the standard deviation. Those factors showing a relatively large number of persons with deviations from the mean exceeding one standard deviation would seem to offer greater possibilities for investigation of the effects of nutritive or physical status. Such factors as changes in pulse rate and serum lactate, bicarbonate, CO_2 tension, sugar, and phosphate during the performance of a moderate fixed task, and changes in systolic, diastolic, and pulse pressures during maximal work would, therefore, appear more fruitful in this respect.

It may be observed that with a few exceptions, notably D. A. and R. W., who represent the two extremes of physical capacity, those children who show the extreme deviations from the mean of a given response when performing moderate work are seldom the children to show the extreme deviations when performing maximal work. It may also be observed that, in the case of most of the factors measured, there is a greater variability of response to moderate than to maximal work, as judged by the greater number of persons showing more than one standard deviation from the mean. In interpreting the data, it should be borne in mind that, while the amount of moderate work performed by each subject is the same for all of the children, the actual effort put out by the individual child in performing this work probably varies more than it does when each child is making the maximal effort, but with varying success.

In these experiments the average rise in pulse rate and in systolic pressure increases slightly as the work is changed from a moderate to a maximal character. The maximum pulse rates under either condition are considerably lower than those found by Robinson during walking

TABLE IV

CHANGES DURING EXERCISE

FACTOR MEASURED	MODERATE WORK						MAXIMAL WORK					
	MEAN $\overline{\Delta}$	STANDARD DEVIATION	EXTREME DEVIATIONS FROM MEAN				MEAN $\overline{\Delta}$	STANDARD DEVIATION	EXTREME DEVIATIONS FROM MEAN			
			ABOVE		BELOW				ABOVE		BELOW	
			SUBJECT	Δ-$\overline{\Delta}$	SUBJECT	Δ-$\overline{\Delta}$			SUBJECT	Δ-$\overline{\Delta}$	SUBJECT	Δ-$\overline{\Delta}$
Pulse rate, beats per min.	+57	±17	M. G. R. H.	+21 +20	D. A. R. W. J. Bo.	−25 −21 −19	+64	±19	J. Ba.	+38	W. P. R. W.	−34 −20
Systolic pressure, mm. Hg	+30	±11	M. G.	+13	R. H.	−28	+34	±14	R. W. P. P.	+22 +21	R. H. D. A.	−23 −18
Diastolic pressure, mm. Hg	−11	±12	J. Ba.	+17	R. H.	−25	− 6	±13	R. B. F. C.	+24 +14	J. G. R. H.	−21 −15
Pulse pressure, mm. Hg	+40	±13	M. G. D. A.	+20 +16	J. Ba.	−22	+40	±14	R. W. P. P.	+26 +15	R. B. D. A. J. Ba.	−18 −16 −15
Hemoglobin, Gm./100 c.c.	+0.5	±0.4					+0.8	+0.4	J. G. R. B.	+0.8 +0.5	R. W.	−0.7
Serum protein, Gm./l.	+3.0	±1.2	M. G. P. P.	+2.1 +1.5	R. W.	−1.8	+4.2	±1.2	J. G.	+1.6	R. W.	−3.1
Cell volume, %	+1.3	±0.7	P. P.	+0.8	R. W. J. G.	−1.4 −1.0	+2.6	±1.0	J. G.	+1.2	R. W.	−2.6
Blood sugar	+0.23	±0.35	R. H. D. A.	+0.73 +0.57	J. G. F. C.	−0.45 −0.38	+0.22	±0.43	D. A.	+1.11	F. C.	−0.68

Serum phosphate, meq./l.	+0.10	±0.08	D. A. J. Ba.	+0.16 +0.10	F. C. L. S.	−0.09 −0.09	+0.13	±0.06	D. A.	+0.14	R. H. F. C.	−0.08 −0.07
Serum pH	0.00	±0.03			D. A.	−0.09	−0.12	±0.06	R. W. J. Bo.	+0.11 +0.11	D. A.	−0.08
Serum bicarbonate, meq./l.	−4.1	±2.3	R. W. F. C. L. S.	+3.7 +3.3 +2.8	R. H.	−3.5	−6.2	±1.7	R. W. P. P. J. Ba.	+2.0 +1.9 +1.8	R. B. J. G.	−3.4 −2.0
Serum bicarbonate, at initial pH, meq./l.	−4.2	±2.8	R. W. F. C.	+4.7 +3.7	D. A. R. H.	−3.8 −3.4	−9.3	±2.7	R. W.	+4.7	R. B. J. G.	−5.3 −3.5
Serum lactate, meq./l.	+3.5	±2.1	R. H. D. A.	+3.4 +2.4	R. W. L. S. F. C.	−3.1 −2.8 −2.5	+7.8	±2.4	R. B.	+5.6	R. W.	−4.0
Serum CO_2 tension, mm. Hg	−7.2	±4.2	D. A. F. C.	+5.9 +4.7	J. Bo. J. G.	−6.6 −4.6	−2.1	±6.6	D. A.	+12.2	J. Bo. R. W.	−13.1 −7.6
Serum chloride, meq./l.	+0.7	±0.4	R. H.	+0.9	M. G.	−0.7	+0.1	±0.9	L. S.	+1.8	D. A. R. B.	−1.7 −1.2
Serum Σ anions, meq./l.	+1.0	±0.8			J. G. J. Bo. R. B.	−1.6 −1.2 −0.9	+1.8	±0.9	L. S. J. Ba.	+1.4 +1.1	J. Bo. R. W.	−1.3 −1.2
Serum sodium, meq./l.	+0.3	±1.0	R. W. D. A.	+1.5 +1.6	W. P. F. C.	−1.4 −1.1	+1.0	±1.2	J. G. R. B.	+2.4 +1.4	L. S.	−2.3

or running. Diastolic pressure shows great variability of response. In the majority of subjects it decreases during moderate exercise, but in some persons a rise occurs. There is a greater tendency for diastolic pressure to rise with the performance of maximal work. The average rise in pulse pressure is the same after both moderate and maximal work, but analysis of the individual cases shows a great variety of response as the work is changed from a moderate to a maximal character.

A study of the nutritive status and physical capacity of those persons who show extreme deviations from the mean reveals little relation of any cardiovascular response to either of these factors. It is perhaps suggestive that the children showing extremely high deviations from the mean in cardiovascular responses to moderate work were fair or poor in physical capacity; the two children showing the lowest rise in pulse rate with maximal effort were of good or superior physical capacity, while the two showing the lowest rise in systolic pressure were fair or poor. R. H. is exceptional in showing little change in systolic pressure and a marked fall in diastolic pressure with both moderate and maximal effort. His physical capacity is only fair. His response to moderate work is characterized also by an unusually high rise in pulse rate and in serum chloride, sugar, and lactate.

The most striking changes in the blood during exercise occur in the lactate and the bicarbonate concentrations. Fig. 1 shows the rise in lactic acid for all of the individual experiments. The experiments for a given child are grouped together and the children are arranged from left to right in the order of their decreasing physical capacity as measured by their performance on the bicycle. The single experiments conducted at weekly intervals show little evidence that a training factor has affected the lactic acid response, such as was observed by Schlutz and Blish[1] in experiments conducted daily. Each child shows a fairly uniform response from one experiment to the next, which characterizes him as an individual and reveals his physical capacity to a marked degree. The three children who show very little change in lactic acid when performing moderate work are those who show superior performance on the bicycle when maximal effort is called forth. Our results on the child support the work of Dill, Talbott, and Edwards[17] on adults in showing that the extent of the lactic acid and bicarbonate changes during the performance of a fixed task furnishes an excellent guide to the capacity of the person for physical activity.

With maximal effort, the rise in lactic acid is higher in every case. The very high values reached by J. G. and R. B. would seem to indicate that they put forth more effort than the others in trying to accomplish what for them was impossible.

We had hoped that a study of the lactic acid changes during exercise might give further information as to the extent to which the physical capacity of the child might be limited by his nutritive state. Schlutz

and Blish found no definite relation between the extent of the lactic acid rise during exercise and the nutritive status of the child, although the few children who showed large lactic acid rises were undernourished children. In the present investigation, many of the higher rises in lactic acid with moderate work occur in thin children. Two other undernourished children on whom single experiments were run before it was discovered that they were unsuitable to continue the experiments also showed higher lactic acid rises when performing the same fixed task. On the other hand, not all of the thin children give high lactic acid responses with moderate work, and one of the higher rises is shown by an obese child (J. Bo.).

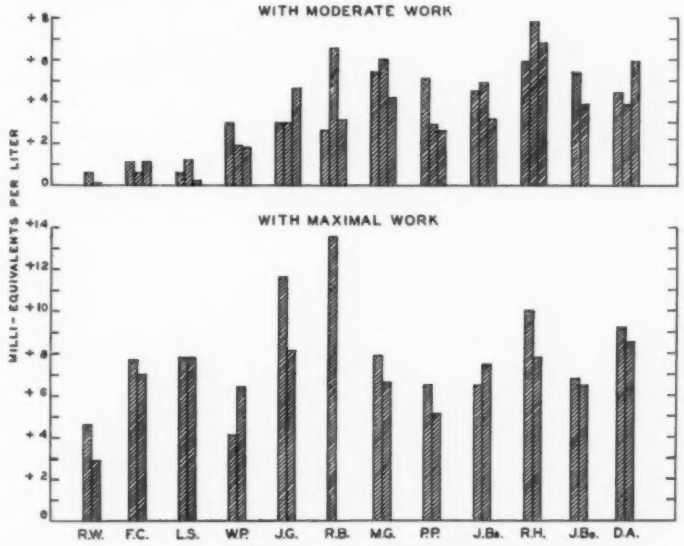

Fig. 1.—The rise in serum lactate resulting from the performance of (a) fifteen minutes of moderate exercise at a fixed rate of work, and (b) one minute of exercise at a maximal rate.

The individual experiments for a given child are grouped together for each set of conditions. The children are arranged from left to right in the order of their decreasing physical capacity as measured by their performance on the bicycle.

The lactic acid rise when a fixed task is being performed would presumably be dependent upon both the mechanical efficiency of the person and his capacity to supply oxygen to the tissues. Either of these factors might depend upon training and, therefore, in a child, upon age. The lactic acid responses to exercise shown by the brothers and sisters in the group are pertinent to this question. In the case of the brothers, the younger one is clinically well developed and well nourished, while the older one is thin and small for his age, but two years older. The performance of the older boy on the bicycle is better, and his lactic acid response is smaller. The two sisters present practically the same pic-

ture. One is a year older than the other, small for her age and thin. Her sister is larger and heavier for her build and less thin. The older girl performs better on the bicycle and shows a smaller lactic acid rise with moderate exercise. It would seem that age and training are far more important factors than the nutritive state of the child in determining his physical capacity, and that physical capacity is dependent upon many interrelated factors, only one of which is nutrition.

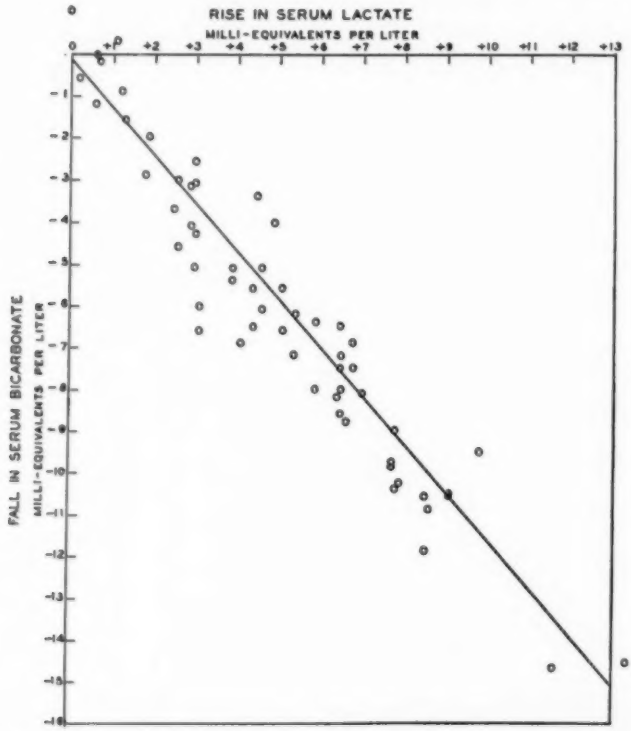

Fig. 2.—Correlation between the rise in serum lactate and the fall in serum bicarbonate (at initial pH) during exercise. The equation of the line drawn through the points, $[LA^-]_s = -0.17 - 0.85\ [HCO_3^-]_s$, was determined by the method of least squares.

The fall in serum bicarbonate with exercise approximates inversely the rise in lactic acid. Fig. 2 shows the relation between the two for all of the individual experiments. The bicarbonate concentration at the end of exercise has been corrected by means of the relation $\frac{-\triangle\ [HCO_3^-]_s}{\triangle\ pH_s} = 28^{18}$ for any change in pH which may have occurred. In the great majority of experiments, the fall in bicarbonate exceeds the rise in lactate by a small amount. The equation $[LA^-]_s = -0.17 - 0.85\ [HCO_3^-]_s$, represents the relation between the two as calculated by the method of least

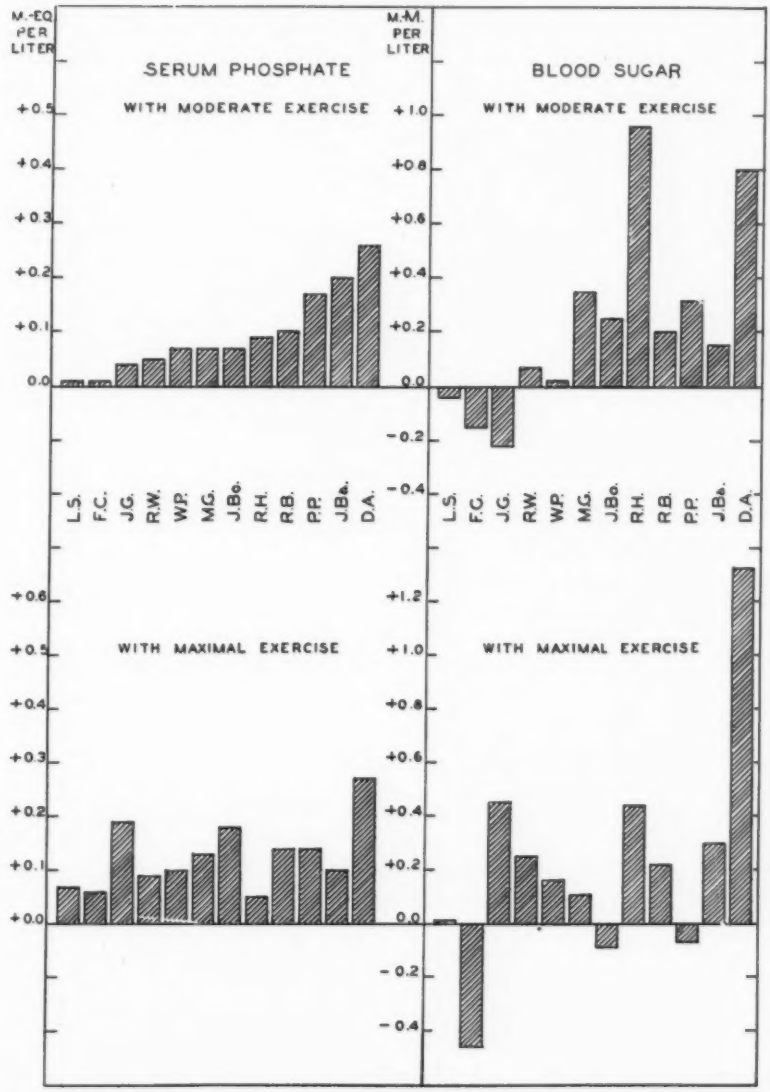

Fig. 3.—Changes in serum phosphate and blood sugar resulting from the performance of (a) fifteen minutes of moderate exercise at a fixed rate of work, and (b) one minute of exercise at a maximal rate. The results for a given child have been averaged.

squares. This fairly constant relation justifies the use of serum bicarbonate values corrected to initial pH as an approximate measure of the entrance of fixed acid into the blood in experimental work with children in cases in which small samples of finger blood are necessary or desirable.

During moderate work, pH changes are negligible except for a fall of 0.09 in the case of D. A. During maximal work, a marked fall in pH occurs in all except two cases, J. Bo. and R. W. Serum CO_2 tension, calculated from serum pH and bicarbonate by means of the Henderson-Hasselbalch equation, falls significantly during moderate work except in the cases of four boys of superior or good physical capacity (R. W., F. C., L. S., and W. P.) and one boy of very poor capacity (D. A.). With maximal work D. A. shows a marked fall; the others show little change either way. Since changes in pH and CO_2 tension during exercise are regarded as the resultant of two factors, overventilation and entrance of fixed acid into the blood, these results indicate that during moderate exercise all of the children who show a rise in serum lactic acid are able to compensate by overbreathing with the exception of D. A.; but during maximal work, on the contrary, only R. W. and J. Bo. can compensate. D. A. is a thin, neurolabile child, and R. W. and J. Bo. are both well nourished.

The effects of exercise on serum phosphate and sugar are represented for the individual children in Fig. 3. In the upper half of the chart, representing the results for moderate work, the children are arranged for convenience from left to right according to the increasing magnitude of the phosphate rise. For maximal work they are arranged in the same order as above. The rise in phosphate with both moderate and maximal effort is small, reaching a maximum of 0.27 meq. in the case of D. A. Those children showing the smaller, often insignificant rises in phosphate during moderate exercise are children of superior or good physical capacity. These children also show little change or a slight fall in blood sugar during moderate exercise, while the others exhibit a rise which becomes marked in the cases of R. H. and D. A. One boy, F. C., well-nourished, shows a significant fall in blood sugar with maximal exercise. It is of interest that three of the four boys who possess an adequate or excessive amount of fatty tissue show at least a slight fall in blood sugar during maximal exercise.

The protein concentration of the serum increases with moderate effort. The magnitude of the rise, varying from 1.5 to 6.6 per cent, is characteristic of the individual child, but bears no apparent relation to his nutritive state, his physical capacity, or the magnitude of his blood pressure rise. With maximal effort protein concentration increases still further, from 1.4 to 7.2 per cent, and the individual differences tend to disappear.

The changes in the concentrations of the diffusible ions of the serum, notably sodium and chloride, are very slight during both moderate and

maximal work. The chloride concentration shows a very slight rise during moderate work in all but one of the children (M. G.). While this slight rise, usually about 0.7 meq., falls within the limits of error of the method, its consistent recurrence and the fact that analyses were performed with great care and in triplicate would seem to give it significance. With maximal effort no consistent rise in chloride concentration is observed, a result which may be accounted for by the counter-effects of the chloride shift from serum to red cells which is associated with the fall in pH. In these experiments the sodium concentration does not change consistently in either direction during moderate work, but under the conditions of maximal effort, it shows a slight rise in all but two children. Since the changes in sodium concentration scarcely exceed the limits of error of the method, these findings are suggestive, but of doubtful significance.

SUMMARY

The effects of exercise have been studied intensively in twelve children from 11 to 13 years of age. The study has included determinations of the changes in heart rate and systolic and diastolic pressures, resulting from both moderate and maximal work on the bicycle ergometer, and determinations of the changes in many of the blood components under the two conditions of work. An attempt has also been made to relate these changes to the nutritive status and to the physical capacity of the child.

The nutritive status of each child has been established by clinical examination, by the weight and fat indices of McCloy, and by creatinine indices. Physical capacity has been measured by performance on the bicycle ergometer.

With the exception of serum pH and sodium during moderate work and diastolic pressure, blood sugar, serum chloride, and CO_2 tension during maximal work, all of the factors measured showed significant changes as the result of exercise.

Pulse rate and systolic pressure increased with exercise, but as work was changed from a moderate to a maximal character little further increase occurred, as a rule. Diastolic pressure showed great variability of response under either condition of work, decreasing in the majority of children during moderate exercise, but showing an increased tendency to rise during maximal exercise.

Hemoglobin, red cell volume, and serum protein increased with both moderate and maximal exercise. With one exception (R. W.), the magnitude of the rise was greater during maximal exercise, the maximum increase for an individual child reaching 8.2 per cent for protein, 8.6 per cent for cell volume, and 10.4 per cent for hemoglobin.

The sodium and chloride concentration of the serum showed little change, although an increase of approximately 0.7 meq. in chloride during moderate exercise appears to be significant.

Serum phosphate increased during both moderate and maximal exercise by a small amount not exceeding 0.3 meq. The rise in phosphate tended to be higher during maximal work. Blood sugar showed small variable responses to exercise but increased slightly in the majority of persons.

Serum lactate increased, on the average, by 3.5 meq. during moderate exercise, and by 7.8 meq. during maximal exercise. Serum bicarbonate, corrected to initial pH, showed a corresponding, but slightly greater, fall. The pH did not change appreciably during moderate exercise but decreased on the average, by 0.09 during maximal work.

Greater variations in response occurred during moderate work in pulse rate and serum lactate, bicarbonate, CO_2 tension, sugar, and phosphate, and during maximal work in systolic, diastolic and pulse pressures. These factors would, therefore, appear to offer more fruitful fields for investigation of individual differences and their relation to physical capacity.

The present investigation was limited to too small a number of children and too heterogenous a group to enable us to draw conclusions, but a few relationships appear suggestive. Superior physical capacity is indicated in the child, as well as in the adult, by the lack of a significant rise in serum lactic acid and a corresponding fall in bicarbonate when a fixed moderate task is performed. Those children showing the smaller, often insignificant, rises in phosphate during moderate exercise possess good or superior physical capacity. These children also show little change or a slight fall in blood sugar under such conditions while the others exhibit a rise which may become marked. The children showing the higher cardiovascular responses to moderate work are only fair or poor in physical capacity.

While nutritive status undoubtedly has some effect upon the physical response of the child, many other factors complicate the problem. Many more children will have to be studied and the various factors interrelated in some statistical manner before much progress can be made in the solution of the problem. We feel, however, that the methods used in the present investigation offer valuable tools for its solution.

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CONGENITAL ARTERIOVENOUS FISTULAS IN CHILDREN

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VASCULAR anomalies have been recorded in medical literature for many centuries. They represent congenital defects in the vascular tree which may be observed at birth or which may manifest themselves later in life. Perhaps the simplest type of vascular anomaly is represented by the so-called port-wine mark, while the type of anomaly that is the most complicated and most far-reaching in its effect is the arteriovenous fistula.

All of these vascular anomalies are of special interest to pediatricians, since most of these conditions are noted at birth or in early life. The simple vascular nevi are easily recognized, although many of the more complicated lesions are not fully understood. Cases of congenital arteriovenous fistula are frequently unrecognized by both pediatricians and surgeons. Most of the cases observed at The Mayo Clinic had not been correctly diagnosed prior to admission. Diagnoses such as elephantiasis, gigantism, hypertrophy, "tumor," cavernous hemangioma, and varicose veins have been common. In several instances, poliomyelitis was suspected in the normal lower extremity because it was smaller than the involved extremity.

In most instances, the diagnosis can be established definitely if the symptoms and signs are carefully evaluated. In former years the most obvious cases were recognized at the clinic, while insufficient data were obtained on many other suspicious cases. In recent years more accurate observation and newer diagnostic procedures have greatly increased the number of proved cases.

A certain number of these children can be benefited more definitely if treatment is carried out before great deformity has occurred. It is, therefore, our purpose to help stimulate interest and diagnostic acumen in these conditions, in the hope that more arteriovenous fistulas will be recognized and treated in childhood.

In this description we are assuming that all the vascular anomalies recorded in this article represent varying degrees of abnormal arteriovenous communication. We feel that the term "abnormal arteriovenous communication" is all-inclusive, and we use it to designate all vascular abnormalities in which arterial blood passes into the venous system without having to pass through a capillary bed. Reid[1, 2] and one of us (Horton[3, 4]) have sponsored this thesis for a number of years. In his articles Reid has pointed out that pulsating angiomas, cirsoid aneurysms,

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arteriovenous aneurysms, and even simple angiomas all represent the same fundamental type of lesion. We are in accord with his conclusions that even simple angiomas represent abnormal communications between the smallest arteries and veins. The capillary bed is the normal communication between the arterial and venous systems. Any variation from the normal capillary communication in the direction of dilatation necessarily constitutes an abnormal arteriovenous communication, and one can invariably demonstrate the presence of such a lesion either by means of an increase in oxygen content of venous blood adjacent to such a region or by means of arteriography.

Many modern textbooks on surgery and pathology regard hemangiomas, cirsoid aneurysms, and similar conditions as neoplasms, and even today, probably the prevailing idea is that cirsoid aneurysms are neoplasms. Virchow[5] made the important observation that hemangiomas of the liver could be injected through the hepatic artery or through the main portal or hepatic veins. Several older writers, in operating upon angiomas, have noted that the veins contained arterial blood. Warren,[6] for example, in 1858, while amputating an arm for a varicose aneurysm, noted that the veins carried arterial blood, and he later demonstrated that the veins anastomosed freely with the arteries. This same phenomenon was observed during operation in practically all of our cases. The cases which we are reporting have been selected from the records which have accumulated in the Section on Pediatrics since its establishment in 1921. Approximately 1,000 records were reviewed, and we are presenting forty-four cases from this survey. We have excluded all cases of uncomplicated hypertrophy, gigantism, and lymphedema, and have included only those cases in which there was definite clinical evidence that abnormal arteriovenous communications existed in the involved part. We also have excluded simple vascular nevi, such as port-wine marks, strawberry marks, and spider nevi. Many of our cases exhibited cavernous angiomas.

In this study of forty-four cases, the intracranial vessels were involved in four subjects; the scalp, face and neck in four subjects; the upper extremities in nine subjects; and the lower extremities in twenty-five subjects. In addition, two patients exhibited hemihypertrophy of the entire half of the body. All patients in this report are less than 15 years of age.

INTRACRANIAL VASCULAR ANOMALIES

There were four patients in this group, three boys and one girl (Table 1). Their ages ranged from 3 to 14 years. Signs and symptoms had been present from one month to four years prior to admission to the clinic. An audible bruit was present in all four patients, and in two of these (Cases 1 and 2), a palpable thrill was also present. In three cases (Cases 1, 2, and 3), there were signs and symptoms of an

TABLE I

INTRACRANIAL CONGENITAL VASCULAR ANOMALIES

CASE NO.	AGE (YR.) AND SEX	REGION INVOLVED	AGE AT ONSET OF SIGNS AND SYMPTOMS (YR.)	DESCRIPTION	BRUIT	THRILL	OCULAR FUNDI	ROENTGENOGRAM
1	3, M	Left mastoid	½	Left exophthalmos, hydrocephalus. Pulsations in left mastoid region with thrill and bruit	+	+	Bilateral optic atrophy	Increased pressure, sellar erosion
2	10, M	Left middle cerebral vessels	6	Progressive right hemiplegia. Bruit and thrill over both carotids and most of head	+	+	Normal	Normal
3	14, F	Right suboccipital	13	Bruit behind right ear audible to patient. Disappeared with pressure on adjacent vessels	+	0	Bilateral choked disks	Increased pressure, sellar erosion
4	5, M	Right mastoid	5	Bruit over right mastoid region accidentally found by parents. Disappeared with pressure over right carotid	+	0	Normal	Normal

organic intracranial lesion associated with headache and vomiting. In Cases 1 and 3 there were positive changes in the ocular fundi.

Case 1 exhibited roentgenographic evidence of increased intracranial pressure, with erosion of the sella turcica, left exophthalmos, and optic atrophy. No treatment was carried out on this patient.

Case 2 did not exhibit roentgenographic evidence of increased intracranial pressure, but did have a progressive right hemiplegia with a right homonymous hemianopia. The ocular fundi appeared to be normal.

Case 3 exhibited roentgenographic evidence of increasing intracranial pressure, with erosion of the sella turcica, choked disks, and a subjective sensation of a buzzing noise in the right ear.

The patient in Case 4 had no symptoms whatsoever. A bruit was present over the head, but this had been discovered accidentally by the parents. The fundi appeared normal, and the roentgenographic examination gave normal results. No treatment was carried out, and we have no follow-up information regarding this patient

Treatment.—Surgical exploration was carried out in Cases 2 and 3 by Dr. Craig. In Case 2 a definite arteriovenous fistula was demonstrated in the left middle cerebral vessels. It was not possible to resect this anomaly, and no information has been obtained about this patient since dismissal.

An absolute diagnosis was not established in Case 3, although the surgical exploration revealed numerous dilated arterial and venous channels present over the right suboccipital region, without definite evidence of communication with the extracranial vessels. The right occipital artery was ligated and other vessels were coagulated. After surgical exploration, the bruit was no longer audible, and the patient's symptoms improved. We have no information as to the present status of this patient.

VASCULAR ANOMALIES OF THE SCALP, FACE, AND NECK

Four patients presented signs and symptoms of vascular anomalies involving the scalp, face, and neck, without evidence of intracranial involvement (Table II). Three of these patients were boys and one was

TABLE II

CONGENITAL VASCULAR ANOMALIES OF THE SCALP, FACE AND NECK

CASE NO.	AGE (YR.) AND SEX	REGION INVOLVED	DESCRIPTION	MAXIMAL SURFACE TEMPERATURE	
				INVOLVED REGION	NORMAL REGION
5	9, F	Right side of neck, face, and scalp; right ear	Extensive cavernous hemangiomas; multiple bruits and thrills	Felt warmer	
6	2, M	Right mastoid	Enlarged veins. Bruit ceased with pressure over adjacent vessels		
7	4, M	Right side of neck	Bruit above right clavicle disappeared with pressure over right common carotid	35.7° C.	34.6° C.
8	7, M	Right side of neck	Pulsation; bruit above right clavicle disappeared with pressure over right common carotid		

Bruit and thrill were present in all cases. Ocular fundi and roentgenograms of the head were normal in Cases 5, 6, and 8, and were not recorded in Case 7.

a girl. The right side of the face, neck, scalp, and ear was involved in Case 5, the right mastoid region in Case 6, and the right side of the neck in Cases 7 and 8. A continuous bruit and thrill were present in each case. There was a definite increase in surface temperature of the involved side in Cases 5 and 7, but no information was recorded from this standpoint regarding the other two cases. Extensive birthmarks were present in Case 5, but were absent in the other three cases. In Case 5

(Fig. 1), the examination showed extensive cavernous hemangiomas from the right clavicle to the right parietal region and involving the entire right ear. This region felt definitely warmer than the opposite side. Several separate bruits and thrills were present, indicating multiple abnormal arteriovenous fistulas.

Fig. 1.—A large vascular anomaly occupied the right side of the head and neck and the right ear. A loud continuous bruit could be heard over this region, and a palpable thrill was present.

In Case 6, the continuous bruit, which was heard over the right mastoid region, disappeared when pressure was applied over the right occipital and the right posterior auricular artery. The superficial veins of the scalp in this region were enlarged.

In Cases 7 and 8, a continuous bruit was detected above the right clavicle when these patients were being examined for unrelated conditions. In each case, pressure over the right common carotid artery caused the bruit to cease.

Treatment.—In Case 5, the surgical treatment by Dr. Adson consisted of ligation of the right external carotid artery, followed by the ligation and excision of numerous dilated vessels over the mastoid region. The right transverse cervical artery was also ligated. The condition of the patient was definitely improved after operation and further operations are planned in the future.

In Case 6, the right occipital artery was ligated by Dr. Craig, many dilated veins were coagulated, and several large communicating sinuses in the cranial bones were occluded. This patient showed improvement after operation; the bruit was markedly decreased in loudness and was heard only occasionally.

In Cases 7 and 8, no treatment was advised. These patients were asked to report at regular intervals, but their subsequent course is unknown.

VASCULAR ANOMALIES OF THE UPPER EXTREMITIES

In nine subjects an upper extremity was involved, the right in three instances, and the left in six instances (Table III). Five of the subjects were boys, and four, girls; their ages ranged from 1 to 10 years. All of these lesions were first noted at birth. The involved extremity was from 1 to 3 cm. longer than the normal extremity in two cases; no increase in length was noted in six cases; and in one case, the humerus in the involved arm was actually 2.5 cm. shorter than that in the corresponding normal arm. This latter condition was most certainly due to the use of radium, which had been applied at intervals over a period of seven years. Nothing of significance was noted in the blood pressure readings in this group of cases. Cardiac hypertrophy was noted in one case (Case 10), and a positive bradycardiac reaction (that is, a slowing of the heart rate after closure of the arteriovenous fistula) was noted in two cases. Bruits and thrills were not observed in this group of cases.

Fig. 2.—A large vascular mass of spongy consistency in the region of the left elbow.

Arteriographic studies were carried out in Case 9 and indicated the presence of abnormal arteriovenous communications. These communications were too small to permit the development of a bruit. An increase in surface temperature of the involved extremity was recorded in three cases. The greatest increase in surface temperature was 2.8° C. No record or note was made regarding the surface temperature in the other cases. Oxygen determinations of the venous blood in the

TABLE III

CONGENITAL VASCULAR ANOMALIES OF THE UPPER EXTREMITIES

CASE NO.	AGE (YR.) AND SEX	REGION INVOLVED	DESCRIPTION OF INVOLVED EXTREMITY	BRADYCARDIAC REACTION*	OXYGEN SATURATION OF VENOUS BLOOD (%)	
					INVOLVED EXTREMITY	NORMAL EXTREMITY
9	10, M	Right forearm	Superficial and deep veins dilated and tortuous. Surface temperature increased		77.6	76
10†	2, F	Left axilla and arm	Larger and warmer with diffuse port-wine mark. Surface temperature increased 2.8° C. above that of the normal extremity	6		
11‡	8, F	Left side of chest, left arm and forearm	Bluish-red birthmarks			
12§	9, M	Left extremity	Hand enlarged with bluish birthmark		88.7	
13	1, F	Right side of chest and entire extremity	Soft spongy mass of chest and axilla. Extremity large, spongy, discolored with birthmark present			
14	4, M	Left arm, hand, forearm, and fingers	Superficial and deep hemangiomas, with birthmarks	4		
15	4, M	Left arm	Dilated enlarged tortuous veins			
16	7, M	Left forearm, hand, and fingers	Diffuse cavernous hemangiomas, with birthmark			
17	3, F	Right arm	Diffuse hemangiomas; arm larger and warmer. Surface temperature increased			

*Decrease in cardiac rate per minute when fistula was closed by pressure.
†The involved extremity in Case 10 was from 2 to 3 cm. longer than the normal extremity. (Case published previously.)
‡The involved extremity was 1 cm. longer.
§The involved extremity was 2.5 cm. shorter.

involved extremity were carried out in two cases, but the results were conclusive in only one of these cases. Birthmarks were present in seven of the nine patients.

All of the children showed a marked similarity in the general appearance of the involved extremity (Fig. 2). In practically every instance the involved extremity was larger. Frequently, there was an increase in the growth of hair, as well as increased sweating in the affected region. Dilated and tortuous vessels and enlarged hemangiomatous regions were present in all instances, and these findings were very prominent in a few cases.

Treatment.—Four subjects were treated with radium which was applied over the dilated vessels and angiomatous regions, and two of these four subjects (Cases 12 and 14) also had multiple surgical explorations carried out at the clinic. The surgical treatment consisted of excision of numerous angiomatous regions and ligation of abnormal vessels. Surgical exploration was performed on one subject (Case 9). At this time angiomatous tissue was removed, but no other treatment was given. Two of the patients noted improvement following both radium and surgical treatment. Owing to the widespread nature of the lesion, apparently, none of these patients were actually cured. We have no follow-up information regarding the other subjects.

VASCULAR ANOMALIES OF THE LOWER EXTREMITIES

There were twenty-five subjects in this series, twelve boys and thirteen girls (Tables IV and V). Their ages ranged from 1 month to 14 years. In fifteen cases the right lower extremity was involved, and in ten cases the left lower extremity was involved. The condition was noted at birth in thirteen cases. In the other twelve cases the abnormality of the extremity had been noted from six months to ten years after birth. The involved extremity was longer than the normal extremity in thirteen patients (Fig. 3). Measurements were recorded in eleven of the thirteen cases, while in the other two cases, the involved extremity was stated to be longer than the normal extremity, but no actual measurements were recorded. The greatest increase in length in the involved extremity over that of the normal extremity was 5 cm. In one case (Case 34), the tibia and fibula of the involved leg were actually 3 cm. shorter than the tibia and fibula of the normal leg. These measurements were taken from roentgenograms which included both lower extremities and which were made when the child was 13 years of age. In one instance (Case 22), the involved extremity was generally smaller in circumference, but equal in length and warmer than the normal extremity. This patient had an arteriovenous fistula between the femoral artery and vein, demonstrable by means of arteriography and confirmed at surgical exploration.

The blood pressure was not significant in any of these cases, although cardiac hypertrophy, grade 2, on a basis of 1 to 4, was present in one case (Case 21). An arteriovenous fistula involving the iliac vessels was present in this particular case, and a bruit and a thrill were also present. Of the twenty-five cases, a bruit and a thrill were present in four cases, and a positive bradycardiac reaction was present in three cases. Arteriographic studies were carried out in four cases (Cases 18, 20, 22, and 23). All gave evidence of abnormal arteriovenous communications (Fig. 4). The surface temperature of the involved extremity was increased in ten cases, in six of which it was actually measured. The greatest increase was 5.4° C. Oxygen studies of the venous blood of the involved extremity were carried out in six cases, and a significant increase in the oxygen content of the venous blood was noted in four of the six cases.

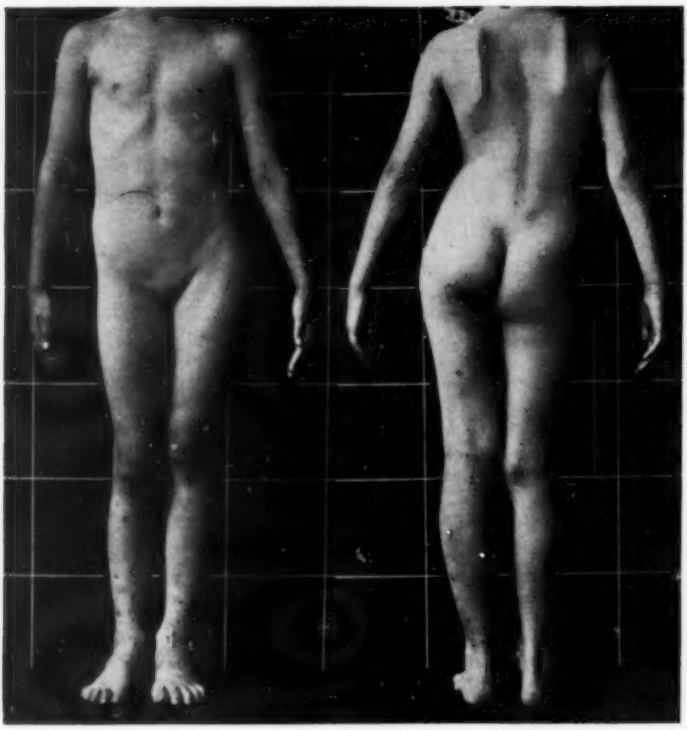

Fig. 3.—Anterior and posterior views showing congenital arteriovenous fistula of the left leg. The leg was larger and longer than the normal right leg.

The involved extremities in this series of cases were strikingly similar. In practically every instance, the abnormal extremity was larger in diameter, and there was an increase in growth of hair and increased sweating. Trophic ulcers were not present in a single instance. These

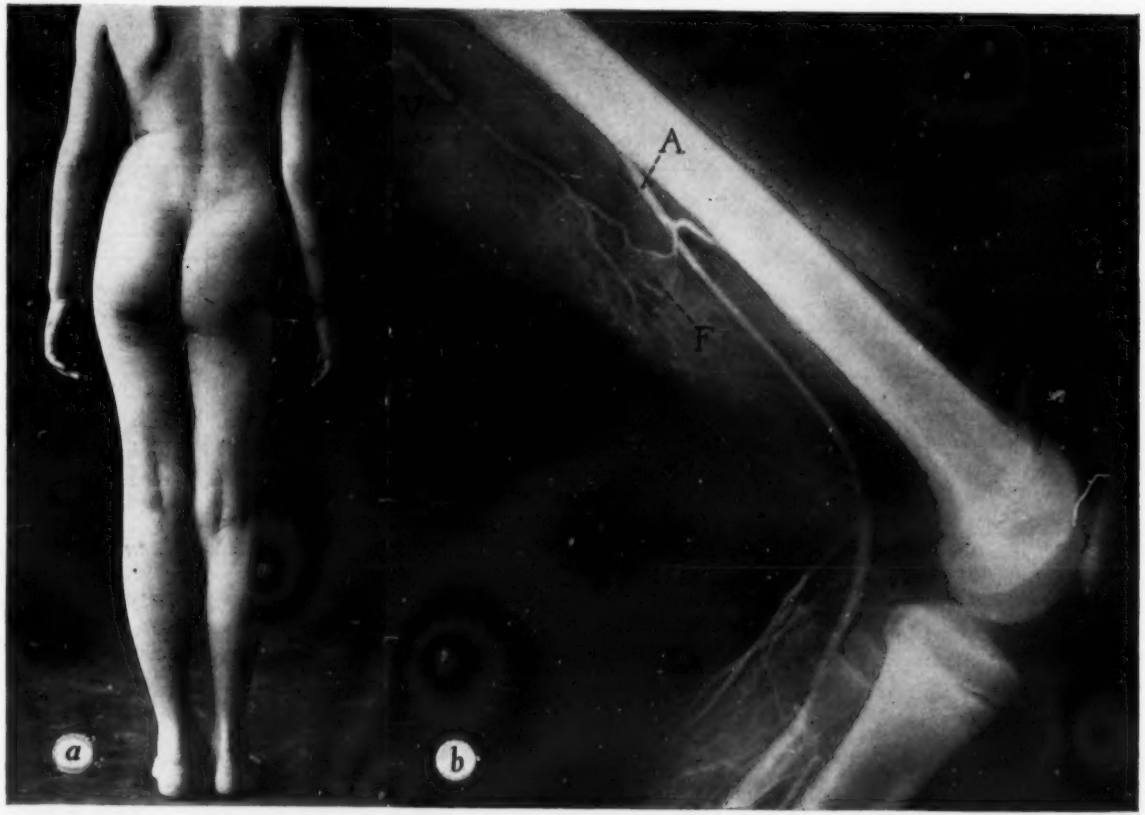

Fig. 4.—*a*, Congenital arteriovenous fistula of the left lower extremity of a girl aged eight years at the time the photograph was taken. No bruit was present. Increase in the length and size of the left lower extremity is evident. *b*, Arteriogram of the left thigh, giving evidence of an arteriovenous fistula which connects the lower third of the femoral artery with an accompanying vein. *A*, artery; *V*, vein; *F*, fistula (after Horton and Ghormley[12]). One of the authors submitted the original film and a slightly retouched photograph, and in the two, the vascular connections apparently were identical. The retouched photograph was employed because therein the contrast was better.

TABLE IV

HISTORY AND GENERAL EXAMINATION OF CONGENITAL VASCULAR ANOMALIES OF LOWER EXTREMITIES

CASE NO.	AGE (YR.) AND SEX	REGION INVOLVED	AGE SYMPTOMS BEGAN (YR.)	INCREASE IN LENGTH OF INVOLVED EXTREMITY (CM.)	DESCRIPTION OF INVOLVED EXTREMITY	BIRTH-MARK	BRUIT	THRILL
18*	7, F	Left extremity	7	3.8	Longer, larger, and warmer throughout	0	0	0
19*	5, M	Right leg	5	1.9	Longer, larger, and with increased vascularity	0	+	+
20	14, M	Left foot	10	1	Pulsating mass over second and third metatarsals. Increased vascularity	0	+	+
21	12, M	Right extremity	Birth	Longer	Longer, larger, warmer. Thrill and bruit over groin. Increased vascularity	+	+	+
22*	10, M	Left extremity	4	0	Smaller, warmer, with increased vascularity	0	0	0
23	7, F	Left extremity	3	5	Longer, larger, warmer. Markedly increased vascularity	0	0	0
24	14, M	Right extremity	6	0	Larger, with markedly increased vascularity	+	0	0
25	10, M	Right extremity	Birth	0	Warmer. Markedly increased vascularity. Venous sacs	+	0	0
26	10, F	Right leg	Birth	2.5	Longer, larger. Dilated venous sinuses	0	0	0
27*	9, F	Left leg and foot	4	4.2	Longer, larger, with increased vascularity	0	0	0
28*	4, F	Left leg and foot	Birth	1.2	Longer, larger, warmer, with markedly increased vascularity	0	0	0
29	14, F	Left extremity	Birth	2.5	Longer, larger, with markedly increased vascularity and sweating	+	0	0

*Published previously.

30	11, M	Right extremity	Birth	Longer	Longer, larger, with markedly increased vascularity and sweating. Flexion contracture	+	0	0
31	⅓, M	Right extremity	Birth	0.5	Longer, larger, with markedly increased vascularity	+	0	0
32	3, F	Right leg and ankle	1	1.2	Longer, larger, with markedly increased vascularity	0	0	0
33	11, F	Right thigh	3	2.4	Vascular mass removed from popliteal space elsewhere before admission	0	0	0
34	1/12, F	Right leg	Birth	-†	Three times normal size; markedly increased vascularity	+	0	0
35	14, F	Right thigh	Birth	0	Larger; hemangioma middle third of thigh; increased vascularity	+	0	0
36	13, M	Left leg	10	0	Calf larger	0	0	0
37	6, M	Left extremity	Birth	0	Larger, with increased vascularity	+	0	0
38	5, F	Right extremity	1	0	Larger, with increased vascularity and sweating. Venous sacs	+	0	0
39	8, F	Right leg	Birth	0	Larger, with increased vascularity and sweating	+	0	0
40	2, M	Left extremity	Birth	0	Larger, with dilated venous spaces, and markedly increased vascularity	+	0	0
41	8, M	Right thigh	½	0	Middle third of thigh larger, with increased vascularity	+	0	0
42	8, F	Right extremity	Birth	0	Larger, with pulsating veins and deep spaces and increased vascularity	0	0	0

†The right tibia and fibula were 3 cm. shorter than the corresponding bones of the normal extremity at 13 years of age.

TABLE V

SPECIAL EXAMINATIONS OF CONGENITAL VASCULAR ANOMALIES OF LOWER EXTREMITIES

CASE NO.	BLOOD PRESSURE (MM. MERCURY)	BRADY-CARDIAC REACTION	MAXIMAL SURFACE TEMPERATURE (°C.)		OXYGEN SATURATION VENOUS BLOOD (%)		ARTERIOGRAMS	ROENTGENOGRAMS
			INVOLVED EXTREMITY	NORMAL EXTREMITY	INVOLVED EXTREMITY	NORMAL EXTREMITY		
18	110/80	6	35	33.5	91.7	62.7	Arteriovenous fistula, femoral vessels	Left tibia and fibula longer
19	75/25		35.1	31.5	76	31		Normal
20	130/60		Felt warmer				Arteriovenous fistula, dorsalis pedis vessels	Region of destruction in second metatarsal
21	132/75		Felt warmer					
22	116/74		Felt warmer				Arteriovenous fistula, femoral vessels	Phleboliths
23	110/80		Felt warmer				Arteriovenous fistula, anterior tibial vessels	Left tibia 2.5 cm. longer
24	120/70		31	30	89.6	86.5		Normal
25	88/60		35.9	30.5	70.4	58.7		Phleboliths
26	102/60	8			68.7	64.7		Right tibia and fibula longer
27	116/70		33.1	28.1	91	46		All bones larger and longer
28	100/68	12	32.9	31.1				Left femur and tibia longer
29								Normal
30								Normal
31								Right tibia 5 cm. longer
32	100/45							Normal
33	130/90							Phleboliths (elsewhere)
34								1920, negative; 1933, right tibia 3 cm. shorter
35	140/80							Normal
36	130/85							Normal
37	100/60							Normal
38	120/80							Phleboliths
39								Normal
40								Normal
41								Normal
42	90/58							Phleboliths

almost invariably develop later in life. There was evidence of increased vascularity in nearly every case. In many instances, the dilated tortuous vessels were prominent, and in several patients these dilated venous sacs were observed to pulsate. The presence of a pulsating venous sac always indicates the presence of an arteriovenous fistula. Many cases exhibited large, thin-walled, dilated venous sacs and angiomatous-like tissue which was of a spongy character and easily compressible (Fig. 5). When the

Fig. 5.—Enlargement of superficial veins with hemangiomatous masses of the right leg. The photograph was made with infrared technique.

involved extremity was elevated, the venous engorgement frequently disappeared to a marked extent and reduced the size of the extremity greatly. In most instances, the venous blood seemed to be under increased pressure. When the extremity was elevated, the veins collapsed less readily at heart level than did the veins of the normal extremity. In one patient (Case 25), practically all the soft-tissue structures in the foot seemed to be replaced by dilated, thin-walled venous sacs which were

readily compressible. The pelvic structures, as well as the scrotum and penis, were involved in this case (Figs. 6 and 7). Except for the increase in the length of the long bones in a few instances, nothing of significance was observed in roentgenologic studies, other than the presence of numerous phleboliths and swellings of soft tissue. Erosion of the second metatarsal bone was noted in one case (Case 20).

Fig. 6.—Marked increased vascularity of the thigh, leg, and penis, with dilated venous sacs.

Treatment.—Nine of the twenty-five subjects in this group had radium treatment, and two of the nine also had surgical exploration at the clinic; one patient had excision and ligation of vessels in the thigh and calf of the involved extremity (Case 22). A good result was reported two years later. The second patient (Case 29) had a tenotomy of the hamstring muscles and later an osteotomy of the femur to correct a deformity. Definite improvement was noted in this case. In addition, two patients

(Cases 26 and 33) had excision of large veins prior to admission to the clinic. No surgical treatment was carried out for these patients, and we have no follow-up information regarding them. One of them had apparently been cured prior to admission here.

Fig. 7.—A roentgenogram of the pelvis of the patient shown in Fig. 6, showing multiple phleboliths with mottling of soft-tissue shadows by the vascular anomalies.

Four additional patients (Cases 18, 20, 28, and 41) had surgical explorations here, with excision of accessory vessels and angiomatous tissue. One of these four later had an amputation of the foot through the metatarsal region. A good functional foot was noted six years later. One patient (Case 18) had ligation of an arteriovenous fistula between the femoral artery and vein. Another (Case 20) had ligation of an arteriovenous fistula which involved the dorsalis pedis artery. An excellent result was obtained in this case. Another (Case 41) had a large angiomatous region (7 by 15 cm.) removed from the middle one-third of the right thigh. No follow-up information was obtainable with reference to this case. One patient (Case 30) had an amputation above the knee here at the clinic because the involved extremity was so deformed that it was useless. This patient died at home a year later. The exact cause of his death was not stated.

The patient in Case 35 was first observed when 14 years of age. At the clinic she had repeated roentgen and radium treatment over the right

thigh. When finally observed at the age of 21 years, she had evidence of a malignant neoplasm in the involved extremity, and she died at home a few months later, with evidence of widespread metastasis.

Fig. 8.—Hemihypertrophy of the right side of the body illustrates an increase in the size of the right side of the face, as well as an increase in the size and length of the right arm and leg.

When the patient in Case 34 was first observed at the clinic a month after birth, it was noted that the involved leg was three times larger in circumference than the normal leg, but apparently not any longer. She received numerous radium treatments here at frequent intervals over a period of four years. All signs of the vascular anomalies had disappeared when she was finally observed here at 13 years of age. The tibia and fibula in the involved leg were actually measured and were found to be 3 cm. shorter than the tibia and fibula of the normal leg. This shortening

had undoubtedly resulted from the radium treatments over the epiphyseal regions during the growing period.

The patient in Case 37 showed definite improvement after radium treatment. The patient in Case 42 did not show any improvement after the radium treatment, which had been given at intervals over a period of eleven years. This particular patient was last observed in 1938, at which time she was 19 years of age. At that time she had pulsating veins and increasing vascularity of the extremity to a marked degree.

The use of a para rubber bandage to compress the dilated and tortuous veins was advised in five cases. This is the best palliative measure which we have used for decreasing the blood supply to the involved extremity. The patient in Case 19 was treated in this manner, but the involved leg was finally amputated six years later (elsewhere) because of repeated hemorrhages. No further information was available in the other cases.

HEMIHYPERTROPHY OF ONE-HALF OF THE BODY

Two cases of this type were observed, one in a boy 13 years of age, and the other in a girl 6 months of age. The right side of the body was involved in the first case and the left side, in the second. Both conditions had been observed at birth. In the first case there was an irregular capillary nevus over the entire body and extremities (Fig. 8). There was a definite hypertrophy of the right side of the face, the right leg, and the right arm, as compared with the left. The right leg was warmer than the left, and dilated veins were present over this extremity. In the second case there was definite hypertrophy of the left side of the face, left arm, and left leg, as compared with the right side of the body. There was a definite increase in the surface temperature of the involved left lower extremity, and the latter was longer than the corresponding normal extremity. There were three regions with definite capillary nevi present. It seems logical to assume that the presence of the increased vascularity in the hypertrophied side of the entire body may have resulted in an increase in the blood supply to this part, and, hence, the basis for the hypertrophy.

COMMENT

The oxygen studies referred to in this paper were carried out according to the Van Slyke gasometric method.[3, 7] The blood, in each instance, was removed from the vein under oil so that it did not come into contact with the air at any time. In the making of such studies, it is important to have the patient at rest and in a constant environmental temperature room; otherwise, abnormal oxygen content of the veins will be frequently encountered, especially during hot summer weather. Furthermore, it is important always to remove the blood from the corresponding normal extremity, selecting, if possible, a corresponding site so that a comparative study can be made of the oxygen content of corresponding

regions in the normal and in the involved part. Surface temperature studies in this series of cases were also made in constant temperature rooms, with the environmental temperature at 78° F. and the humidity 40 per cent. The electric thermocouple, originally described by Sheard,[8] was used for this purpose.

Arteriography.—Arteriography now affords perhaps the best method of diagnosing early congenital arteriovenous fistula. It was first employed at the clinic in 1932,[9] and most of the arteriovenous fistulas which have been observed at the clinic since that time have been studied in this manner. The technique, as originally described by one of us (Horton), is as follows:[9-13]

"A local anesthetic agent is infiltrated around either the brachial or femoral artery. Ten to twelve cubic centimeters of thorotrast are then injected into the artery while the artery is closed either by the use of a blood pressure cuff (which is promptly inflated above systolic pressure), when the brachial artery is being injected, or by digital pressure just proximal to the point of injection, when the femoral artery is being injected. A 20 gauge needle is satisfactory for this purpose. The thorotrast is injected promptly, and a series of four or five roentgenograms is made in rapid succession while the artery is still closed. In making arteriograms in cases of either congenital or acquired arteriovenous fistula, it is not necessary momentarily to relax the pressure on the artery after exposure of each film because there is a constant leakage of the injected medium from the arterial to the venous system by way of the fistula or fistulas, depending, of course, upon their size; if the pressure is released, the medium is almost immediately carried out of the extremity, and, hence, the arteriogram would be unsatisfactory.

"One can interpret arteriograms properly only when the pathologic physiology of arteriovenous fistula is understood. The injected medium, like the blood, takes the course of least resistance, which is from the artery, through the fistula, to the veins. Even with the brachial or femoral artery closed by pressure proximal to the point of injection of the thorotrast, there is always leakage of the medium by way of the fistula into the veins, and this is invariably present when the first film is exposed. When the normal arterial tree is injected, thorotrast does not appear in the veins in the first film after injection if the artery proximal to the point of injection is kept closed. The demonstration of the opaque medium in the first film with the artery closed, therefore, is diagnostic of arteriovenous fistula. This corresponds, diagnostically, to the finding of arterial blood in the regional veins. The amount of filling by the thorotrast on the venous side is proportional to the size of the fistula or fistulas. If the fistula is large, the opaque medium will pass directly from the artery to the vein with little or no filling of the arterial tree distal to the site of the fistula. If the fistula is small, only a small amount of the medium leaks into the vein. Enough remains in the arterial tree

to visualize it completely. However, it is sometimes difficult to determine whether a given vessel, which has been visualized in a film, represents an artery or a vein. This is attributable to the fact that the normal characteristics of the vein may have been obliterated because it had become arterialized."

Bruits and Thrills.—In acquired arteriovenous fistula, a bruit and a thrill are invariably present, but in congenital anomalies of this character, bruits and thrills are usually absent. This is due to the fact that the abnormal arteriovenous communications are so small that the amount of blood which is short circuited into the venous system is not sufficient to produce disturbances of this character. Hence, if one waits for the development of a bruit and thrill before making the diagnosis of an arteriovenous fistula, he is likely to miss most of the early cases. The presence of a bruit and thrill merely indicates a relatively advanced lesion.

One should have no difficulty in distinguishing between the bruit of an aneurysm and that of an arteriovenous fistula. In the case of an aneurysm, the bruit occurs during systole and entirely fades out before the next systole. In arteriovenous fistula, the bruit persists throughout the cardiac cycle, but is accentuated with each heart beat. One of us (Horton) and Baldes[14] recently introduced a new photographic method for recording bruits. By this method, one can easily distinguish the bruit which is present over an aneurysm from that which is present over an arteriovenous fistula, if he is in doubt after listening over such a lesion with a stethoscope.

The diagnosis of a congenital arteriovenous fistula should be relatively simple if one has this condition in mind when seeing a patient with a vascular anomaly. The involved part, usually the extremity, is invariably warmer than the corresponding normal extremity, and in children, there is almost invariably an increase in the size and length of the involved part. It is important to make an early diagnosis, for, frequently, palliative treatment can be carried out which will help to prevent deformities and other complications which may arise in the course of the development of such an anomaly.

SUMMARY

A study of forty-four cases of vascular anomalies of the arteriovenous type, occurring in children, are recorded in this study. The intracranial vessels were involved in four subjects; the scalp, face, and neck in four subjects; the upper extremities in nine subjects; and the lower extremities in twenty-five subjects. In addition, two patients exhibited hemihypertrophy of an entire half of the body. All patients were less than 15 years of age. The diagnosis of abnormal arteriovenous communications seemed well established in every instance. Methods of diagnosis and treatment are discussed.

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THE TONIC NECK REFLEX IN NEWBORN INFANTS

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THE tonic neck reflex as a characteristic response common to man and quadrupeds was first described by Magnus in 1924. In decerebrate quadrupeds, when the head was turned to the extreme right or left, there followed an extension of the forelimb on the side toward which the head was turned, and flexion of the opposite forelimb.

Magnus observed some twenty-six normal infants from the ages of a few hours to that of 16 weeks, in whom he was unable to induce this reflex. However, he did find that the tonic neck reflex existed in idiots and patients suffering from extrapyramidal tract lesions. He concluded that in man the tonic neck reflex is a pathologic phenomenon.

Gesell reported in 1938 that, according to his observations of infants during their first twelve weeks of waking life, the tonic neck reflex is a normal characteristic spontaneously manifested in the supine position. At 20 weeks, it is normally supplanted by symmetric head and arm postures, and marked persistence of the tonic neck reflex beyond the first half year is indicative of retarded, arrested, or defective development.

In this study, we undertook to determine the occurrence of the tonic neck reflex in newborn infants. During routine examinations of infants in the newborn nursery of the Beth Israel Hospital, two hundred infants between the ages of a few hours and 9 days were tested for tonic neck reflex. Those infants who were crying, sleeping, or sucking on their hands were not tested. The infants tested were in a quiescent supine position, and while so, their heads were rotated gently to the extreme right and left.

Of the two hundred tested, eighty infants (40 per cent) showed the characteristic tonic neck reflex, and one hundred and twenty (60 per cent) failed to respond in that manner. Twenty-seven infants were examined during the first twenty-four hours of life and again on the eighth day. Of these, seven were negative on both days, and six were positive on both days. Eleven were positive on the first day and negative on the eighth day, and five were negative on the first and positive on the eighth day.

In analyzing the totals according to age (Fig. 1), we found that, in fifty-one infants from 1 to 24 hours of age, 51 per cent were positive. Of fifty-nine infants from 1 to 2 days of age, 36 per cent were positive. Twenty-seven infants from 2 to 7 days of age were tested and showed

33 per cent positive. Of fifty-seven infants tested from 8 to 9 days of age, 37 per cent were positive, and of six infants, from 9 to 10 days of age, 18 per cent were positive.

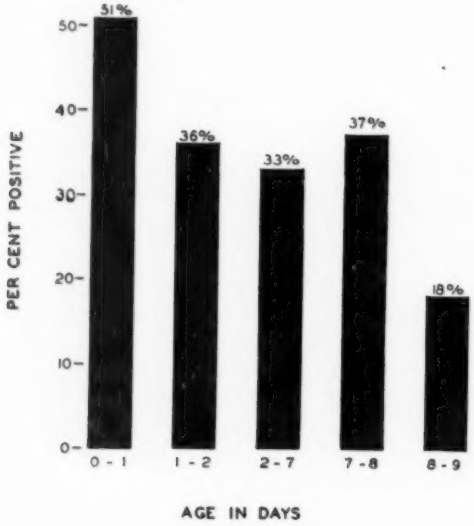

Fig. 1.

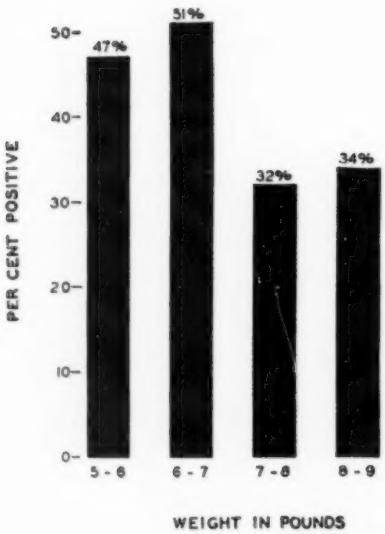

Fig. 2.

The greatest percentage of positive responses was found in the 1- to 24-hour age group, these being 33 per cent higher than the group of from 9 to 10 days of age, and 14 per cent higher than those from 8 to 9 days of age.

As an index of maturity, an analysis of the results according to the weights of the infants was made (Fig. 2). Seventeen infants whose weights were between 5 and 6 pounds were tested. Of these, 47 per cent were positive. Sixty-eight infants between 6 and 7 pounds were tested, and of these, 54.4 per cent were positive. Sixty-seven infants from 7 and 8 pounds in weight were tested, and 32 per cent were found to be positive. Of forty-one infants from 8 to 9 pounds in weight, fourteen, or 34 per cent, were positive.

In this group of two hundred examinations, tests were conducted on two mongolian idiots, one of whom was tested twice. The first infant was positive on the second day of life; the second infant was positive on the first day of life and negative on the seventh day.

COMMENT

In order to obtain infants who can be tested for the tonic neck reflex, it is necessary to observe them for long periods at a time when they are awake and quiet, or to observe only those infants who, at the time of examination, are in this condition. Even under ideal conditions, they may respond momentarily with a quick movement of extension of one or both arms. We took as positive only those who maintained the position of extension of the forearm on the side to which the head is turned and flexion of the opposite forelimb, for a period of more than two seconds.

Following these conditions, we found that, as a clinical test, the tonic neck reflex was of questionable value.

CONCLUSION

Forty per cent of two hundred newborn infants who were tested for tonic neck reflex showed the characteristic response of extension of the forelimb on the side toward which the head was turned.

Forty-one per cent of the positive reactions occurred in infants less than 2 days of age.

Twenty-seven infants who were tested twice, once during the first day and again on the eighth day, showed inconstant responses.

Both positive and negative results were elicited in the two mongolian idiots tested.

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THYROID THERAPY IN JUVENILE MYXEDEMA

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PROBABLY no ordinary glandular deficiency is more frequently overlooked than myxedema, especially in its juvenile form. This is unfortunate, because nothing in therapy succeeds much more brilliantly than does thyroid medication in juvenile myxedema.

Since the recognition of the role of the growth hormone of the pituitary gland, a tendency has arisen to regard an element of pituitary deficiency as universally present in all cases of infantilism. With this idea in mind, it has become the custom with many physicians to treat these cases of dwarfism with a mixture of hormones in which the pituitary products are employed generously, but in which the thyroid medication is given only in small and inadequate amounts. However, in juvenile myxedema the deficiency is one of the thyroid alone, and thyroid medication only is indicated. Pituitary products are not usually necessary. In fact, their addition may befog the issue at times and lead to ineffective management unless the amount of thyroid is kept sufficient. However, if true indication for pituitary products exists, obviously they should be employed, but not at the expense of thyroid therapy.

Two patients in point are presented, both of whom, in my opinion, were suffering from juvenile myxedema. In infancy both were regarded correctly as cases of hypothyroidism. Later both patients were placed in the hands of specialists who looked upon them as instances of primary pituitary deficiencies and who placed them on mixed pituitary and thyroid products. On this management neither patient made satisfactory response, but both have experienced phenomenal growth and normal development when given adequate thyroid therapy alone, or mixed treatment in which the thyroid has been maintained at an adequate level.

The first case concerns a dwarfed child who was brought to me at 7 years of age. In the seven months prior to seeing me, she had made practically no growth. Solely on thyroid therapy in adequate amounts, she has grown 20 inches in height and has gained 57 pounds in weight during six and one-half years (Fig. 1).

The second case is in some ways still more remarkable, in that growth has been accomplished still more rapidly and at an older age. It concerns a fat, dwarfed child, 15 years of age, who gained but one-quarter of an inch in one year on a mixture of products administered

From the Philadelphia Institute for Medical Research, Philadelphia General Hospital.

at the hands of an endocrine specialist. This child was lacking nearly a foot in height and was 20 pounds overweight for her height. Now, after twenty-seven months on adequate amounts of thyroid, supplemented by whole anterior substance by mouth, she has gained 10 inches in height and is underweight, rather than overweight, for her height. Pubertal development has proceeded normally also, and menstruation has been established (Fig. 2).

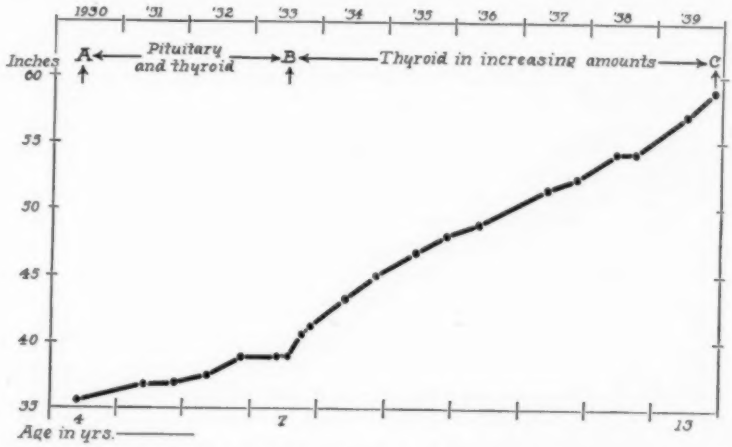

Fig. 1.—Growth curve of patient in Case 1. *A-B* represents three years of mixed treatment with an inadequate amount of thyroid; *B-C*, normal growth from thyroid alone.

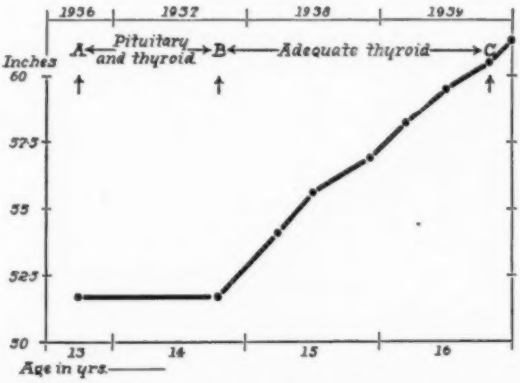

Fig. 2.—Growth curve of patient in Case 2. *A-B* represents the period of mixed treatment with inadequate amounts of thyroid; *B-C*, normal growth on adequate amounts of thyroid supplemented with pituitary therapy.

The case records are as follows:

CASE 1.—A white female, aged 7 years, was brought to me June 24, 1933, because of her obvious lack of growth. The family history revealed nothing of consequence.

The father was tall, and the mother moderately so. The patient had had two attacks of pyelitis, the first at 13 months of age. At 6 years she had had pneumonia complicated by middle ear disease. The patient was said to be mildly anemic. The story of infancy is of special interest. After birth the baby suffered from icterus neonatorum. She was somewhat tardy in development. Her physician, a pediatrician of unusual experience, diagnosed thyroid deficiency and placed her on thyroid extract. The first teeth were cut at 16 months of age, and at about the same time she began to walk. The child appeared unnaturally short. This became more apparent as time passed. She had a peculiar figure—a large torso, sloping shoulders, a protuberant abdomen, and pads above the clavicles and at the base of the neck. She was bright in many ways, rather coy in nature, more at ease with adults, and uninterested in and uninteresting to children of her own age.

The physical examination revealed a grotesque little figure, 8 to 10 inches short of normal, rather ludicrous and somewhat kewpielike in appearance, strange in her actions and reactions. She seemed old beyond her years, resembling a big doll rather than a little girl. Her height was 39 inches, and her weight, 40 pounds. The skin was pale and dry. The heart and lungs were normal. The protuberant abdomen revealed a small navel hernia. The pulse was slow, varying from 70 to 80. The blood pressure was 80/60; the voice was low-pitched, and the basal metabolic rate was said to be normal. The blood count was normal, and the urinalysis, negative.

The parents reported that the child had been under the care of an endocrinologist of national reputation who had made a diagnosis of pituitary and thyroid deficiency and had prescribed pituitary products in abundance with a small amount of thyroid. On this treatment the child had grown only one-eighth inch during the seven previous months, and the parents were rather desperate, fearing permanent dwarfism and possibly something worse. Because of my belief that the child was the victim of juvenile myxedema, she was placed on thyroid extract only (Burroughs Wellcome), 1 grain daily, which appeared to be all that she could tolerate. On this she grew one inch in the next three months, the abdominal protuberance decreased, the voice became clearer and higher, the skin moist, and there was considerable sweating. The pulse rate increased to 108. The parents were delighted with the change in her condition.

During the following year the dose was increased and adjusted as indicated, between 1½ and 2 grains daily. By the end of this year she had gained 4 inches in height and 10 pounds in weight; she also developed a much more normal figure and was beginning to mix with other children. By March, 1935, after twenty-one months, the height gain had been extended to 6¾ inches.

During the next two and one-half years, the family lived in California part of the time and in France for a short period. Growth continued satisfactorily. She improved remarkably from a psychic and mental point of view; she led her class, skipped a grade at school, and now was generally accepted by other children. At 10 years of age she was of good build, and her breasts were beginning to develop.

By June, 1938, after five years of treatment, she had grown 15⅜ inches and weighed 78 pounds. Up to this time her progress had been entirely satisfactory, but during the next six months her height remained stationary, with no growth whatsoever. On inquiry the mother admitted carelessness and stated that during this period the child had had little or no attention and that thyroid therapy had been sadly neglected. Thyroid treatment was resumed, now in doses of 3 grains daily. Growth also was resumed, and the patient grew 3⅜ inches during the following year. Bodily development progressed also.

Now, after six and one-half years, at the age of 13, this girl is of practically normal height, 59 inches tall, weighs 97 pounds, has a good color to her skin, a normal

figure, and well-marked secondary sex characters. She has a normal personality, good scholastic standing, and is accepted as normal by boys and girls of her own age. She still continues to take 3 grains of thyroid (Burroughs Wellcome) daily, with additional vitamins, especially during the winter months. She has gained a total of 20 inches in height and 57 pounds in weight, and has changed from a grotesque, backward, strange child to an entirely normal 13-year-old school girl.

CASE 2.—A white girl, 14 years old, was brought to me in October, 1937, because of dwarfism and obesity. The family history revealed nothing pertinent. The child was born with instrumental delivery. She had always been too fat and was somewhat slow in developing, cutting teeth, sitting up, walking, and talking. Among the past illnesses were included measles, whooping cough, chicken pox, pneumonia, mastoiditis with operation, and tonsillectomy. At the time of her first visit the child was in the eighth grade and was an average student; she liked school but was not very acceptable to the other children because of her lack of height and an innate slowness in thought and action. As time passed, she tended constantly to associate with girls younger than herself. She learned, however, to play the piano and to dance moderately well. She complained of nothing other than coldness, most marked in her hands and feet. Her parents stated that, on a mixture of endocrine products administered at the hands of a specialist, the child had gained but one-quarter of an inch in thirteen months.

The present illness really dated from birth. As an infant she was always too fat, and was a mouth breather with a large and somewhat protruding tongue. Her skin was always pallid. At the age of 4 years hypothyroidism was suspected, and treatment with thyroid extract was started by her local physician.

Physical examination on Oct. 15, 1937, revealed an underdeveloped, fat, pudgy girl, 51⅝ inches tall, weighing 85 pounds, with a dry, pallid, unhealthy, and rather yellowish skin. The findings were negative, except that she lacked about 12 inches in height and was some 20 pounds overweight for her height. Her face was too full, with an open mouth and large tongue. The torso was large with pads above the clavicles and in the breast areas. She showed a typical potbelly. The thyroid area was somewhat full; her hair was rather thick, and her skin, definitely dry. The hands were short, with stubby fingers. Clinically, the picture was that of juvenile myxedema.

The patient was given thyroid tablets (Burroughs Wellcome), 2 to 4 grains daily, pablum, anterior pituitary substance (Armour), 3 grains three times daily, and White's concentrate of vitamin D. The diet was restricted moderately, especially in carbohydrates, and exercise was increased. Within five months she had gained 2¾ inches in height and lost 11 pounds in weight. No untoward effects from the thyroid were noted. Her skin became soft and moist. She sweated much more than formerly and occasionally complained of heart consciousness, especially after running. She became much more active and alert and improved considerably in her school work. At this time it was noted that her breasts were starting to develop and pubic hair beginning to appear. By the end of the year her gain in height had mounted to 4½ inches while her weight had decreased 5 pounds. The thyroid intake was increased to 6 grains daily, and the anterior pituitary substance, to 18 grains daily. Her school work was improving, and she was no longer called "Fatty." At eighteen months, the gain in height was extended to 6⅜ inches, the breasts were enlarging, and she was becoming quite shapely. The pulse was 80, and the blood pressure, 110/70. When she approached 16 years of age, the pituitary substance was increased to 27 grains daily, and injections were started with maturity hormone, 1 c.c., and later 3 c.c., three times weekly. At the end of twenty-seven months she had gained 10 inches (to 61⅝ inches) in height, weighed 107 pounds, and the secondary sex characters and menstruation were well established. Her school work was entirely satisfactory;

her blood pressure remained normal. Recently the pituitary substance by mouth and the maturity complex by injections were stopped, but the thyroid medication is being continued.

The patient is now about on a par with most of her school friends in height, weight, and scholarship, is acceptable to other girls, and is beginning to take an interest in boys. In a little over two years she has passed from a conspicuous thyroid dwarf to an ordinary, well-developed, attractive high-school girl. This has been accomplished without the appearance of untoward effects of any kind. The thyroid therapy, we believe, is largely responsible for the major part of the growth, while the pituitary products, particularly the maturity complex, would seem to have been helpful in bringing on menstruation.

COMMENT

The vital consideration in juvenile myxedema is an adequate supply of thyroid. In addition, careful attention should be directed to all matters pertaining to general health, diet, vitamins, exercise, rest, etc. Pablum is also of considerable value. If other endocrine products are indicated, they should be employed. They should not be used, however, at the expense of thyroid therapy.

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ENVIRONMENTAL AND PERSONALITY PROBLEMS IN THE TREATMENT OF DIABETIC CHILDREN

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INA MAY GREER, IOWA CITY, IOWA

THE introduction of modern methods of treating diabetes mellitus has not only made it possible for diabetic children to enjoy a normal life, but has also brought into the management of diabetic children many problems which have not been given sufficient recognition in the pediatric literature.[1] The necessity for a continuous, strict therapeutic regimen—measuring the diet, administering proper doses of insulin, and giving frequent chemical tests to guard against shock and acidosis—has frequently taxed the resources of both parent and child. Also, in its capacity as a specific, insulin has often given parents a false sense of security, which has resulted in neglect of other factors in treatment. The result has been to bring to the fore, particularly in children from underprivileged families, the importance of environmental and personality problems. Interfering with medical treatment and the satisfactory adjustment of the child to his illness as they do, faulty attitudes of parent and patient frequently have to be corrected. The Department of Pediatrics of the University of Iowa has long recognized the importance of these problems and has referred most of its diabetic children to our clinic. This paper is a study of the problems which these children presented.

CASE MATERIAL

During the twelve years from 1926 to 1938, the Department of Pediatrics of the University of Iowa referred 155 diabetic children to the Department of Psychiatry. Seventeen were under 5 years of age, thirty-nine were from 5 to 10 years old, eighty-six were from 10 to 15, and thirteen were from 15 to 18. Nearly all of the children were indigent cases and from families of the lower economic levels. Intelligence quotients were obtained on all but four, and their I.Q.'s, on the whole, were slightly below the I.Q 's obtained by Terman[2] on 1,000 unselected children. Eighteen were very retarded mentally, seven being morons and eleven having borderline intelligence. Thirty-four were classified as dull normal, sixty-six as average, twenty-one as superior, and twelve as very superior. All were seen at least once by

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the psychiatrist, and many of them (forty-three), several times. Five were admitted to the Psychopathic Hospital for further study or treatment. Pediatric social service follow-up studies were available and reviewed in 139 cases. Of these 155 diabetic children, ninety-four presented problems of psychiatric interest at the time of the first examination. In twelve others, difficulties arose later.

ENVIRONMENTAL PROBLEMS

One of the most common problems faced by the pediatrician and pediatric social worker was the economic inadequacy of the parents. In at least sixty-one families, the supply of insulin or the special diet meant a financial burden, and thirty families at times had to have aid from relief agencies. The social service correspondence is full of stories of valiant efforts to arrange financially for adequate care of the child, and not infrequently the child suffered because the county residence was in doubt or the local relief agency was discouraged with the family.

Extremely unwholesome home environments also very frequently complicated the diabetic treatment. Twenty-two homes were broken by the death of a parent, divorce, separation, or desertion. Fourteen parents were sufficiently inadequate intellectually to make it difficult or impossible to give them a thorough understanding of the management of diabetes. Twenty-four fathers contributed to home instability by misbehavior such as excessive alcoholism, cruelty, shiftlessness, infidelity, or chronic complaining. Fifteen mothers were emotionally very unstable. Five children had to be placed in boarding homes, and foster home placement was considered in several others but could not be carried out.

Parental attitudes which interfered with adequate diabetic treatment were common in this group of children. Frequently, well-meaning but thoughtless parents discouraged the child in cooperation with treatment or in his adjustment to his illness. The prevention and correction of these faulty parental attitudes was one of the principal tasks of the psychiatrist and social worker.

Most parents, of course, were more or less appalled when they discovered that their child had an incurable disease which would always require a most strict and tedious therapeutic regimen. In several the reactions were excessive. One mother collapsed and complained that she would never be able to care for her child. Another felt that she was "going to pieces," and for a while she hired a stranger to take charge of the treatment. One complained that the loss of her home, her financial difficulties, and having a diabetic child were simply more than she could bear; one, whose husband was a diabetic, felt that two diabetics in the family was too much of a strain on her. Not infrequently the mother's fear that she was incapable of learning the diabetic

routine had to be overcome. One mother came to the Children's Hospital quite perplexed and apprehensive because she had been trying unsuccessfully to figure out the proper diet from medical textbooks. In cases such as these, therapeutic efforts were directed toward encouraging the parents and reassuring them of the hopeful prognosis if they cooperated with the pediatricians.

Occasionally a parent was reluctant to accept the diagnosis or the recommended treatment. The father of one 8-year-old girl would not accept the diagnosis, refused to allow insulin to be given, and consulted a quack who put her on a high sugar diet, manipulated her spine three times a week, and assured the parents at each visit that she was getting better and better. Her nutritional state, however, became so serious that the mother finally prevailed upon the father to allow the Children's Hospital to assume care of her. Another mother insisted that the disease could be cured and resorted to patent medicines. It was frequently necessary to warn parents against the use of nostrums and to explain to them why they could not be effective.

The parents of twenty-nine children were uncooperative. Some of them assumed a cooperative attitude in the presence of physicians but did not attempt to carry out recommendations at home. Others were frankly uncooperative. One mother, despite frequent urgings, refused to provide medical attention for her poorly controlled boy, until an acute illness made this imperative. One 11-year-old girl was not returned to the hospital for five years, during which period her diet was not increased. The parents of a 14-year-old girl, who had been told by their family physician that she could not live more than two years, would not bring her back to the hospital for regulation because they had heard that, when patients died in the University Hospital, not only were autopsies performed, but the bodies were turned over to students for dissection. All attempts to shake these parents in this belief were unsuccessful, and, as the home physician had predicted, the girl died in two years. Occasionally parents were resentful and even belligerent when pediatric social workers visited the home.

Another faulty parental attitude which was frequently present to a greater or less degree was an oversolicitous, overprotective one. Before one 12-year-old boy the mother kept saying such things as, "Poor boy, to think that he had to come to this," "Poor child, he'll never be well any more," and "Poor little fellow, I feel that life hasn't much for him now." This mother later, however, behaved more sensibly, and the boy can be used as an example to such mothers because now, seven years later, he is attending college and making an excellent adjustment. One mother kept telling her boy when she gave him his insulin that she wished she could take it for him, and another commiserated with her child because he could not eat everything like other children. Another mother, who treated her 14-year-old boy as if he were an

infant, kept praying for the "light," frequently expressed the hope that she might stay well so she could care for him, and often talked of letting the Lord have his way. When it was pointed out to her that she should rather be encouraging independence and self-reliance in the boy, she said, "Oh, you don't understand; he's my boy." Such parental attitudes sometimes resulted in spoiled-child reactions, so that the child felt abused, refused to stay on his diet, and objected to the insulin. In many cases it also encouraged the child to consider himself an invalid, to resort to physical complaints, and to fail to develop those feelings of self-confidence and self-reliance which are so necessary if he is to overcome his handicap and make a satisfactory adjustment. In this group of diabetic children the parents were routinely urged to treat the child as nearly as possible as a normal child, to assume a matter-of-fact but firm attitude toward his treatment, and to encourage him to take his part in school, athletics, work, and social activities.

An attitude of indifference in the parents was frequently encountered and was often most difficult to overcome. This resulted in carelessness or negligence in carrying out the diabetic regimen. Weighing diets, giving insulin, and testing urine became monotonous after a few months or years, and occasional slight deviations from the routine grew in frequency and proportion until the parents were guessing at the diet, administering insulin irregularly, failing to test the urine, and neglecting to return the child regularly for medical checkups. The importance of conscientious adherence to the routine had to be stressed constantly with some parents, and sometimes an acidosis or serious illness was experienced before they could be shaken out of their indifference.

PERSONALITY PROBLEMS

Perhaps the greatest usefulness of the psychiatrist to the pediatrician in the management of diabetic children is his function of studying the personality of the child, and his efforts to prevent and correct attitudes and behavior in the child, which may interfere with his treatment, happiness, or social adjustment.

The most frequent complaint for which the diabetic child was referred to the psychiatrist was his failure to adhere strictly to his diet. Although these children were given diets which satisfied their needs and contained a wide variety and choice of foods, a fundamental requisite of satisfactory diabetic control was that they eat all of the calculated diet at each meal and no more. Breaking the diet was a more or less serious problem with thirty-seven children. Some stole candy and fruits. Some could not resist the temptation to indulge in delicacies when the opportunity arose at school or at parties. Several who came to the Children's Hospital with a history of stealing

food were on inadequate diets and were actually hungry. One 11-year-old boy had been practically starved for eight years before his admission. He ate everything he could lay his hands on and always admitted it. An 11-year-old girl who was accused of stealing sweets had not been returned to the hospital for five years, and in this time her diet had not been increased. In such cases, the provision of an adequate diet usually solved the difficulty. In others, carefully explaining the reasons for strict diabetic control, appealing to the child's pride and ambition, and placing responsibility squarely on the child were sometimes effective. A 15-year-old boy was most difficult to regulate until the full responsibility for his care was placed upon his own shoulders. His pride seemed touched when he was trusted to send daily reports to the pediatrician. There were a few of these children, however, who seemed to be so utterly irresponsible that no kind of appeal was effective. Several, in addition, presented serious antisocial behavior, and four were committed to training schools.

Fortunately, in only five children was finicalness, dislike for essential foods, or refusal to eat an outstanding complaint. These problems were best handled by a period of hospital training during which the child was removed from an oversolicitous mother and allowed to associate with children who gobbled up their food. Improvement in the general physical condition also tended to improve the appetite.

Although, when they were first seen by the psychiatrist, most of the children seemed to accept their illness without much concern, a few were obviously discouraged and felt seriously handicapped. One 12-year-old girl said that at times she felt like screaming and tearing things up, although she never did so. Another girl said that she might as well be dead as have diabetes, and still another exclaimed, "What's the use? I won't live long anyway." A 17-year-old boy who was referred because for two years he could not be made to stay on his diet or take his insulin regularly said that he didn't see any reason why he should control his diabetes as he didn't care whether he lived or died. This boy, deserted by his mother six years before, felt unwanted in his sister's home and subsequent boarding homes. He was also extremely sensitive about an alopecia totalis which he had had since the age of 3. He felt that nobody cared for him and that everybody stared and laughed at him. He was admitted to the psychopathic hospital and responded nicely to friendly encouragement. His mother was located, arrangements were made for him to live near her and attend an industrial school, and for over a year now he has been cheerful and very conscientious in the regulation of his diabetes. Two children were unhappy because they felt they were financial burdens on their families. Six were ashamed of their diabetes and were inclined to withdraw from social contacts; one girl wanted to stay away from school. Three children objected to taking noon insulin at

school; one of them because he thought the boys would consider him a sissy, and another because he felt the children looked at him in a funny way.

There was the tendency in some children to abandon the struggle by refuge in physical complaints. Several looked upon themselves as invalids, demanded special privileges, refused to face unpleasant situations, and became very badly spoiled. One girl became irritable, bossy, developed a bad temper, and taunted her mother by saying that she could do as she pleased and that her mother could not punish her because she was a diabetic. The mother, after seeking medical reassurance as to this, manually demonstrated the incorrectness of her daughter's theory, and the girl soon ceased to be a problem. Two children feigned shocks in order to control their parents. The treatment of this kind of problem was largely a matter of advising the parents.

Feelings of inferiority and inadequacy were most prone to come to the fore when the adolescent diabetics were beginning to make plans for their lifework. The problem of vocational training has presented itself to the pediatricians in twenty of these 155 children, and the pediatrics department has been making every effort to encourage these young people to make the fullest use of their assets in suitable vocations and doing what it can to help make their training possible. Five have been referred to the state vocational rehabilitation board.

A study of the course of these diabetic children as revealed in the pediatric records indicates that better diabetic control is to be desired. Of 1,150 hospital observations on 100 of these children, followed on the average a little over four years, in only 5 per cent was the diabetes considered by the pediatricians to be well controlled; in 48 per cent it was fairly well controlled; in 41 per cent it was poorly controlled, and in 6 per cent there was practically no control. Approximately one-third of the children could be considered, on the whole, well or fairly well regulated. Another third showed unsatisfactory regulation at times, and about one-third was usually poorly regulated. Twelve of the 155 children are now dead. Such facts present a serious challenge to the child psychiatrist.

CONCLUSIONS

A study of a group of 155 diabetic children shows that, in addition to the purely medical procedures, the treatment of diabetes mellitus in childhood is often complicated by unsound economic conditions, unwholesome home environments, faulty parental attitudes, and poor cooperation and handicapping reactions on the part of the child.

Successful treatment of diabetes in childhood depends upon a long-range, well-planned program which includes: careful evaluation and

treatment of economic, social, home, personality, and behavior problems; thorough instruction of the parents in the management of the child; maintenance of the closest cooperation of parents and child; prevention and correction of faulty parental attitudes, such as discouragement, oversolicitude, and indifference; and, finally, constant encouragement of the child to live a normal, happy, and useful life despite his handicap.

The needs of these children challenge the best that mental hygiene has to offer.

The authors wish to express their indebtedness to the Department of Pediatrics and to the Pediatric Social Service of the Children's Hospital, Iowa City, for the use of their records during the preparation of this paper.

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Critical Review

FLUORINE, MOTTLED ENAMEL, AND DENTAL CARIES

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INTRODUCTION

During the past few years a number of articles, epidemiologic, biochemical, and experimental, have pointed to the possible relation of fluorine to dental caries. This hypothesis is by no means new. In 1892 Crichton-Browne[1] speculated on the possibility that the marked increase in the prevalence of dental caries in the England of that time was due, at least in part, to a deficiency of fluorine in the diet. McClendon,[2] in 1923, theorized that sound teeth probably contain more fluorine than carious teeth, a view which Armstrong and Brekhus[3] have apparently substantiated by chemical analyses.

The causative factor of mottled enamel, fluorine, was not disclosed until 1931,[4, 5, 6] but long before this time curious workers in the mottled enamel field were commenting upon the relationship of mottled enamel to dental caries. The first thorough study of mottled enamel, that of Black[7] and McKay[8] at Colorado Springs and including the Pike's Peak watershed, reported as early as 1916 that, in regard to dental caries, the teeth of these children compare favorably with those of other communities where endemic mottled enamel is unknown. McKay also recorded that mottled enamel in itself did not seem to increase the susceptibility of the teeth to decay, commenting that such a condition is perhaps contrary to what might be expected, considering that the surface of mottled enamel teeth is much rougher than that of normal enamel. Black wrote of the difficulty of successfully filling carious mottled enamel teeth and stated that, although the percentage of carious teeth is less than in nonendemic areas, probably a greater proportion of filled teeth is eventually lost because of the difficulty of retaining fillings in the hypoplastic tooth structure.

The qualitative aspects of this phenomenon have also been discussed by workers of other countries. Masaki,[9] who has studied mottled enamel in the southwestern part of the Japanese archipelago, states in the English abstract of his original report: "It is also remarkable that the percentage of dental caries is comparatively small among those who suffer this abnormality." The number of observations upon which this generalization was based is not stated in the abstract. The lessened prevalence of dental caries among children in the endemic areas of Maldon and Heybridge, Essex County, England, has been reported by Ainsworth.[10] He states that the condition of the teeth of the 214 children examined in the Council schools at Maldon and Heybridge was generally good and well above the average for Council schools.[11] He specifically notes that "there was relatively little caries: 7.9 per cent of the perma-

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nent teeth were carious, as compared with an average in all districts examined of 13.1 per cent; and 12.9 per cent of deciduous teeth were carious against 43.3 per cent in all districts." These percentages are reported[11] as corrected for age.

Mottled enamel in the Argentine Republic has been studied extensively by Erausquin.[12] He states that there appears to be an inverse variation between dental caries and "dientes veteados," the name by which endemic dental fluorosis (mottled enamel) is known in the Argentine. He adds, however, that the findings were not conclusive on the basis of the limited number of areas studied.

EARLY MOTTLED ENAMEL-DENTAL CARIES STUDIES

Two studies restricted to the mottled enamel-dental caries relationship were made in that period prior to the discovery of the etiological factor of mottled enamel, fluorine.

The first attempt to study specifically dental caries in an endemic mottled enamel area was that of Bunting, Crowley, Hard, and Keller in 1928.[13] This study* was made at Minonk, Ill., a community whose domestic water supply several years later was found to contain 2.8 parts per million of fluorides (F).[14] No conclusions were drawn from the survey other than "the behavior of dental caries and the presence of *B. acidophilus* in the mouth are somewhat different to those which exist in other localities." Bunting and his associates further recorded: "In regard to the prevalence of dental caries among these children the percentage of those affected was about the same as would be found in any community, but although caries occurred in the mouths of most children, its extent and activity were remarkably limited. The great majority of cavities consisted of small pit and fissure lesions in the molars, and

TABLE I*

VARIATION IN PREVALENCE OF DENTAL CARIES IN NORMAL AND MOTTLED ENAMEL TEETH OF THREE ENDEMIC AREAS, ACCORDING TO MCKAY

LOCALITY	NO. OF CHILDREN EXAMINED†	TOTAL NUMBER OF PERMANENT TEETH EXAMINED	NUMBER OF TEETH EXAMINED AND PERCENTAGE WITH DENTAL CARIES				
			TEETH	ALL TEETH		MOLAR TEETH	
				NUMBER EXAMINED	PER CENT CARIOUS	NUMBER EXAMINED	PER CENT CARIOUS
Towner, Colo. (pop. 154, 1930)	55	1,264	Normal	879	11	254	36
			Mottled enamel	385	9	101	33
Bruneau, Idaho (pop. 481, 1930)	54	1,142	Normal	356	16	126	46
			Mottled enamel	797‡	8	213	29
Pima Indian School, Sacaton, Ariz. (pop. unstated)	78	2,178	Normal	283	22	99	57
			Mottled enamel	1,895	14	529	45

*Pub. Health Rep. 53: 1443, 1938.

†Age, sex, color, continuity of residence, and constancy of exposure to the mottled enamel-producing waters are not recorded in the report.

‡Presumably, eleven deciduous teeth were included in this total (797); all other teeth referred to are apparently permanent teeth.

*In addition to the authors, others who took part in this study were: Frederick S. McKay, New York City; Frederick Noyes and E. H. Hatton, Chicago; Philip Jay, Rochester, N. Y., and Martha Jones of California. The bacteriologic studies were carried out in duplicate, one by the Michigan group, the other by Dr. Philip Jay.

seldom did caries extend beyond that stage. In this respect the behavior of dental caries in the mouths of these children is distinctly different to that which usually occurs."

Their introductory remark—"that there may be some principle in the drinking water which either inhibits the activity of dental caries or protects the teeth from injury"—takes on an added significance in the light of what is to follow in this paper in the section devoted to experimental caries and biochemistry.

In 1929, McKay[15] attacked the hypothesis that "defective" enamel structure predisposed to dental caries by citing as evidence the observation that mottled enamel teeth, which probably constitute "the most poorly constructed enamel of which there is any record in the literature of dentistry," do not appear to show any greater liability to dental caries than do normally calcified teeth. McKay's report refers to the studies at Minonk, Ill., previously referred to; those at Bauxite, Ark.; Towner, Colo.; Bruneau, Idaho; and the Pima Indian School at Sacaton, Ariz. Certain tabulated data from the three last-named places are included in McKay's report; Table I has been compiled from certain of these data.

EXPERIMENTAL CARIES AND BIOCHEMISTRY

The first instance of the production of carious-like lesions in a rat's molar teeth by means of experimental feeding is generally attributed to Shibata,[16] who fed a diet containing unground rice and greens mixed with various sugars. That coarse ground corn meal will produce similar lesions was first shown by Hoppert, Webber, and Canniff.[17] The etiology of this induced rat caries has been studied extensively by Rosebury, Karshan, and Foley; the major findings of their numerous papers have been summarized recently by Rosebury.[18] These investigators and several others have collected much data with respect to dietary variations, including minerals, vitamins, fats, carbohydrates, and proteins as factors in the rat's response to a caries-producing diet. From the evidence thus far presented, it may be concluded that the production of experimental caries in rats is modified to a greater or less degree by the factors studied, but it has not been demonstrated that these factors generally offer much prospect as significant agents in a far-reaching control of human dental caries.

It remained for Miller[19] to show rather strikingly that induced rat caries may be largely prevented by additions of sodium fluoride or calcium fluoride or iodoacetic acid to the rat's food and water. Miller thus demonstrated for the first time that it is possible to inhibit induced caries in rats by means of two substances noted for their antienzymatic qualities. Prior to Miller's publication, there had appeared in the literature (Fosdick and Hansen,[20] Klein and Palmer,[21] and Dean[22]) speculations as to caries prevention by fluorine in drinking waters, acting as an enzyme inhibitor of any carbohydrate degradation which might be involved in human tooth decay. Miller's results with respect to fluorides have been confirmed by Finn and Hodge.[23*]

*With regard to the reports of Miller, Finn and Hodge, and Cheyne, attention might be called to the fact that some doubt may arise as to the effects obtained until the rat's molars have been carefully diagnosed as in ground sections or in decalcified sections.

Some further light has been thrown upon the mechanism of fluoride prevention, as well as upon the etiology of rat caries itself, by study of the oral flora of the rat. Thus Harrison[24] has reported a temporary reduction of lactobacilli from 18 per cent to 3 per cent and 1 per cent in terms of the total acidogenic organisms associated with iodoacetic acid and fluoride feeding, respectively. Harrison[25] reported on more studies of this nature at the 1939 Annual Meeting of the American Association for the Advancement of Science, and in the abstract of his paper, he states that the inclusion of fluoride and iodoacetic acid "resulted in a sharp decrease in the numbers of lactobacilli cultivable from tooth surfaces." He further adds: "The cultures obtained from suspensions of ground normal rat teeth correspond with surface cultures in the variety and proportions of microorganisms. The flora of teeth in which cavity development was inhibited by fluoride or iodoacetate approximated that of normal teeth. Although in the *surface flora* lactobacilli and perhaps staphylococci appeared to be associated with the development of caries, streptococci predominated in cultures of ground tooth suspensions when gross carious cavities were present."

A reduction of induced rat caries by replacing whole milk powder with casein in the diet has been reported by Lilly,[26] but not confirmed by Finn and Hodge.[23] The possibility of contamination of his casein by fluorine is suggested in Lilly's results in view of the article of Hodge, Luce-Clausen, and Brown[27] reporting fluorosis in rats due to fluorine contamination in a batch of commercial casein.

The role of the saliva in caries prevention by fluorine feeding may be assessed in part by the report of Cheyne,[28] who found that in the absence of saliva (rats with extirpated salivary glands) fluoride is still an effective inhibitory agent.

The significance of the results recently presented by Cox, Matuschak, Dixon, Dodds, and Walker[29] as regards fluorine in the diet remains somewhat in doubt. By means of data covering the incidence of caries in the offspring of female rats, with and without small additions of fluorine in their diet, Cox and his associates seek to show that caries resistance is "built into the enamel" by fluorides. This hypothesis would appear to need more adequate demonstration. It has been shown that rats fed at an age when their molars are almost completely erupted and calcified do not develop carious lesions under fluoride feeding. It is not to be overlooked in these regards also that iodoacetic acid, a caries-preventive, probably does not become a part of the enamel. At present it would seem that quantitative epidemiologic studies involving populations exposed to waters of high fluoride concentration during the period of tooth calcification, followed by exposure during the posteruptive period to waters low in fluorides, and populations whose teeth calcified while they were using waters practically free of fluorides, followed during the posteruptive tooth period by exposure to high fluoride waters, are needed to clarify this question as it relates to human populations.

Until results were presented by Armstrong* and Brekhus[3] with respect to the fluorine content of human enamel and dentine, there was no certain evidence of any relationship between the chemical composition of enamel and dentine and the tooth's resistance to dental caries.

*See also an earlier report of Armstrong on the fluorine content of enamel and dentine of sound and carious teeth (Proc. Am. Soc. Biol. Chem. 8: 5, 1937).

According to these workers, the enamel of sound teeth has a mean fluorine content of 0.0111 ± 0.00203 per cent fluorine, while the enamel of carious teeth contains 0.0069 ± 0.00111 per cent fluorine. Dentine showed less striking differences; dentine of sound teeth equaled 0.0169 per cent fluorine, as compared with carious teeth dentine which contained 0.0158 per cent fluorine. Even in the same person Armstrong and Brekhus found sound enamel to contain approximately 40 per cent more fluorine than carious enamel.

From a study of results recently reported, it might be argued that the enamel with more fluorine is resistant by virtue of a lessened solubility (Volker[30]) and also an acquired antienzymatic property (Bibby and Van Kesteren[31]).

At present it is apparent that there exist at least two different hypotheses, not widely divergent, however, respecting the anticaries property of fluorides. The one looks to the content of fluorine in the enamel to provide for a more acid-resistant or antienzymatic tooth material; the other relies upon a more direct surface phenomenon, possibly antienzymatic or bactericidal, due to fluorides in food deposits or in contact with tooth surfaces. Much experimental work remains to be done before the mechanism of this prevention is understood.

EPIDEMIOLOGIC STUDIES

In 1938, Dean[32] pointed out an inverse variation between endemic dental fluorosis (mottled enamel) and dental caries. Observations made in six cities on a selected sample of 236 9-year-old children continuously exposed to waters of different fluoride concentration, with the history of exposure personally verified in each instance by an interview with the child's parent, indicate a higher percentage of caries-free children in those communities where the domestic water supplies contain higher fluoride (F) concentrations than in communities using waters with lower fluoride content. This relative freedom from dental caries was present (a) in deciduous teeth as well as the permanent teeth, and (b) whether or not the child showed macroscopic evidence of mottled enamel. The pertinent data of this study are shown in Table II.

TABLE II

NUMBER AND PERCENTAGE OF CARIES-FREE 9-YEAR-OLD CHILDREN OF SIX SELECTED CITIES, CLASSIFIED ON THE BASIS OF CONTINUOUS EXPOSURE TO DOMESTIC WATER OF LOWER AND HIGHER FLUORIDE CONCENTRATION

FLUORIDE (F) CONTENT OF PUBLIC WATER SUPPLY IN PARTS PER MILLION	TOTAL NUMBER CHILDREN EXAMINED	CARIES-FREE CHILDREN					
		ALL TEETH		PERMANENT		DECIDUOUS	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
0.6-1.5*	114	5	4	30	26	13	11
1.7-2.5	122	27	22	60	49	38	31

*Original report notes that water supply listed as 1.5 (East Moline, Ill.) may be subject to correction to 1.3 parts per million.

It is a well-known fact that deciduous teeth are seldom affected with mottled enamel. In the data shown in Table II, only three children, all of Colorado Springs (2.5 parts per million), showed even the mildest type of mottled enamel in their deciduous teeth, generally in

the second deciduous molars. Of the 122 children in the higher fluoride water group, 60 were caries-free with respect to the permanent teeth. Of these 60, 33, or 55 per cent, were affected with mottled enamel. In the whole group (122), the incidence of mottled enamel was 53 per cent. These observations suggested that the limited-immunity-producing factor present in the water was operative whether or not the tooth showed macroscopic evidence of mottled enamel.

The disclosure of an inverse relation between the prevalence of dental caries and the fluoride concentration of the domestic water supply in children *with a verified continuity of exposure* raised the question of the kind of relationship between these two variables in larger and general population groups. From Public Health Bulletin No. 226[33] (a dental survey of school children from 6 to 14 years of age made in twenty-six States in 1933-34), the dental caries rates of 8,148 South Dakota white children from 12 to 14 years of age were computed and correlated with the geographic distribution of endemic dental fluorosis in the state.[34] Briefly, the study showed that, in the four counties and the city of Aberdeen where mottled enamel is generally prevalent, an examination of 1,902 white children, from 12 to 14 years of age, disclosed 201 carious permanent teeth per 100 children. In the intermediate group of seven counties where the mottled enamel distribution is uneven and at times sporadic, the examination of 2,765 children showed 314 carious permanent teeth per 100 children; and in the third group consisting of seven counties and the cities of Huron and Sioux Falls, where no endemic areas are known to exist, an examination of 3,481 children showed 415 carious permanent teeth per 100 children. These data indicated that the amount of dental caries in this particular population was inversely proportional to the prevalence of mottled enamel.

The same method of study was applied to the data pertaining to 4,945 white children, from 12 to 14 years of age, of eight Wisconsin cities. In seven cities where the public water supply contained fluorides (F) in amounts ranging from 0.1 to 0.5 parts per million, the amount of dental caries was double and treble that recorded for Green Bay where the water supply contained 2.3 parts per million of fluorides (F).

EPIDEMIOLOGIC STUDIES IN ILLINOIS

A report in 1939 by Dean, Jay, Arnold, McClure, and Elvove[35] lent much additional support to the fluorine-dental caries hypothesis. Because of the marked influence of this study on the fluorine-dental caries problem, it will be described in some detail. The survey included four Illinois cities: Galesburg and Monmouth where the communal water supply contains 1.8 and 1.7 parts per million, respectively; and the nearby cities of Macomb and Quincy where the common water supplies are relatively free of fluorides (0.2 part per million). At Galesburg and Quincy, stimulated saliva samples were collected from approximately 200 children in each city, and a quantitative estimation of the *Lactobacillus acidophilus* was made. In addition, saliva samples of 145 children of these two groups were forwarded to the National Institute of Health for a determination of the amylolytic activity.

Plan of Study.—Factors such as age, sex, and color are known to influence the amount of dental caries in a given group of children. Ex-

tensive experimental work in the field of nutrition, including controlled human experiments, point to diet, especially the carbohydrate intake, as a factor of importance. Factors such as latitude and sunlight have been suggested by some.[36-38] In planning this survey, an attempt was made to take account of these variables in so far as possible. The clinical examinations were limited to 12-, 13-, or 14-year-old white children, *with continuity of risk of exposure to the variable being studied.* It was thought that the magnitude of the sample at Galesburg and Quincy and the inclusion of practically all children possessing the requisites of continuous exposure at Monmouth and Macomb would largely equalize dietetic variations within the groups. The proximity of the cities themselves, located as they are in the flat prairie country of

Fig. 1.—Location of the four Illinois cities.

the western part of north central Illinois, should largely eliminate differences in sunlight intensity. A five-year summary of the available data concerning the number of clear, partly cloudy, and cloudy days discloses a general uniformity in this type of climatologic data. In 1930 the populations of Galesburg, Monmouth, Macomb, and Quincy were approximately 88, 91, 97, and 93 per cent, respectively, native white.

Common Water Supplies.—The common water supplies at Galesburg and Monmouth are obtained from wells drilled to the Cambrian sandstone. The wells at Galesburg are 2,414 feet deep; those at Monmouth, 2445 feet deep. Macomb and Quincy use treated surface water supplies. The Macomb water supply is obtained from the Lamoine River

and from an impounded reservoir known as Spring Lake; Quincy uses treated Mississippi River water. All water supplies have been in use for a period greater than the age of the group examined. As has been previously noted, the Galesburg and Monmouth waters contain 1.8 and 1.7 parts per million of fluoride (F); those of Macomb and Quincy, 0.2 part per million.

Sampling Procedure.—On the day of sampling there were present in the Galesburg Junior High Schools 1,059 12-, 13-, and 14-year-old children. About 70 per cent, or 743, were pupils in the two schools where the study was made. Of these 743, about 42 per cent, or 319, were examined. At Monmouth and Macomb all 12-, 13-, and 14-year-old children with a history of continuous use of the public water supply either since birth or since 6 years of age were examined. At Quincy there were 876 12-, 13-, and 14-year-old children present on the day of sampling in the Junior High School and the five elementary schools included in the study. Of these 876 children, 408, or about 47 per cent, gave a history of continuous use of the city water either from birth or 6 years of age. Of these 408, 306 were examined.

Clinical Examinations.—All examinations were made by a dentist using a mouth mirror and explorer, with the child seated facing a window. Examination of each child consumed about ten minutes' time.

TABLE III

A SUMMARY OF THE INCIDENCE AND AMOUNT OF DENTAL CARIES IN SELECTED 12- TO 14-YEAR-OLD WHITE CHILDREN OF FOUR ILLINOIS CITIES

CITY	NUMBER OF CHILDREN EXAMINED	CHILDREN WITH ONE OR MORE CARIOUS PERMANENT TEETH		CHILDREN WITH CARIES-FREE PERMANENT TEETH		NUMBER OF CARIOUS PERMANENT TEETH PER 100 CHILDREN			
						AGE IN YEARS, LAST BIRTHDAY			
		NO.	%	NO.	%	12	13	14	TOTAL
(a) 696 children with history of continuous use of public water supply									
Galesburg	243	155	63.8	88	36.2	177	207	201	194
Monmouth	99	63	63.6	36	36.4	115	213	271	208
Macomb	63	54	85.7	9	14.3	315	422	367	368
Quincy	291	279	95.9	12	4.1	563	615	732	628
(b) 885 children examined, including those in (a) and those who have continuously used the city water since 6 years of age; water history prior to 6, variable									
Galesburg	319	207	64.9	112	35.1	182	226	196	201
Monmouth	148	96	64.9	52	35.1	150	200	266	205
Macomb	112	96	85.7	16	14.3	346	411	453	401
Quincy	306	294	96.0	12	4.0	567	623	740	633

*Pub. Health Rep. 54: 862, 1939.

Findings.—In Table III are shown the number of children examined, the number and percentage of those with one or more carious permanent teeth, the number and percentage of those who are caries-free, and the number of carious permanent teeth per 100 children. In computing an index for showing the amount of dental caries in these population groups, it was decided to express the amount of dental caries in terms of the number of carious permanent teeth per 100 children examined. The number of carious permanent teeth (both past and present) was determined by combining the aggregates of the number of times the fol-

lowing items were recorded on the clinical examination form: untreated dental caries, extraction indicated, extracted teeth, and filled teeth. The sum of these four aggregates was then divided by the number of children examined, and the quotient was multiplied by 100.

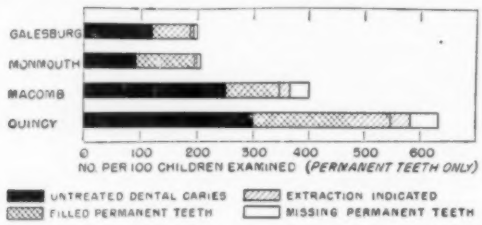

Fig. 2.—Distribution of the four signs indicative of past or present dental caries, classified according to the number per 100 children. (Pub. Health Rep. 54: 862, 1939.)

A graphic illustration of how much each of the four items contributed to the dental caries rates of each city is shown in Fig. 2.

Worthy of special comment is the fact that approximately 35 per cent of the children examined at Galesburg and Monmouth showed no evidence whatsoever of dental caries in their permanent teeth, an unusually high percentage for school children of this age group.

Interproximal or Smooth Surface Dental Caries.—An unusual difference* was noted in interproximal or smooth surface caries. Using the eight surfaces of the four superior anterior teeth for illustrative purposes and limiting the comparisons in all four cities to only those children who used the city water supply continuously throughout life, the 2,718 approximal surfaces in Galesburg and Monmouth showed only 0.59 carious lesions per 100 surfaces. In Macomb and Quincy in 2,814 surfaces there were 8.9 carious lesions per 100 surfaces, or about 16 times as much of this particular type of dental caries in Macomb and Quincy as in Galesburg and Monmouth. These differences are shown in Table IV.

TABLE IV

AMOUNT OF DENTAL CARIES IN THE INTERPROXIMAL SURFACES OF THE SUPERIOR ANTERIOR TEETH OF SELECTED CHILDREN OF FOUR ILLINOIS CITIES

CITY	NUMBER OF CHILDREN EXAMINED*	NUMBER OF PROXIMAL SURFACES	NUMBER OF CARIOUS SURFACES	DENTAL CARIES PER 100 SURFACES
Galesburg	243	1,934	13	0.67
Monmouth	99	784	3	0.38
Macomb	63	502	36	7.20
Quincy	291	2,312	215	9.30

*The histories of these children show continuous use of the municipal water throughout life.

Relation Between Mottled Enamel and Dental Caries.—At Galesburg the incidence of mottled enamel was 46.9 per cent in the 243 school children whose histories indicated continuous use of the city water. The

*An unusual freedom from dental caries in the anterior teeth of Indian children has been reported by Arnim, Aberle, and Pitney (J. Am. Dent. A. 24: 478, 1937). This phenomenon, too, was apparently associated with the use of waters containing more than one part per million of fluoride (F).

amount of dental caries in the 114 children with mottled enamel was 200 per 100 children; in the 129 children listed as not having mottled enamel, 186 per 100 children. It would appear that the factor responsible for the low amount of dental caries in Galesburg was operative irrespective of whether or not the child showed macroscopic evidence of mottled enamel. A previous study[32] on 9-year-old children indicated that the same phenomenon is operative with respect to deciduous teeth, teeth which ordinarily are free of mottled enamel.

TABLE V

SUMMARY OF THE INCIDENCE AND AMOUNT OF DENTAL CARIES IN THOSE CHILDREN FOR EACH OF WHOM A SINGLE LACTOBACILLUS ACIDOPHILUS EXAMINATION WAS MADE

CITY	NUMBER CHILDREN EXAMINED	CHILDREN WITH ONE OR MORE CARIOUS PERMANENT TEETH		CHILDREN WITH CARIES-FREE PERMANENT TEETH		NUMBER OF CARIOUS PERMANENT TEETH PER 100 CHILDREN			
						AGE IN YEARS, LAST BIRTHDAY			
		NO.	%	NO.	%	12	13	14	TOTAL
Galesburg	186*	114	61.3	72	38.7	170	192	223	189
Quincy	209†	201	96.2	8	3.8	518	638	745	636

*176 of the group were those with continuous histories.
†204 of the group were those with continuous histories.

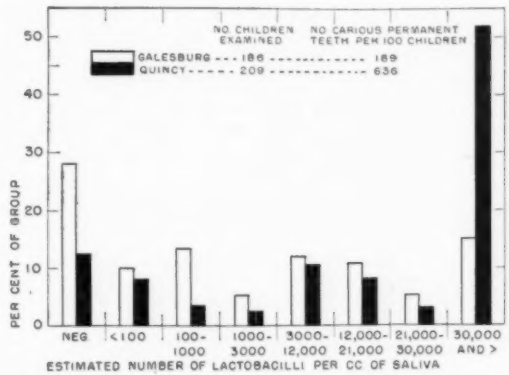

Fig. 3.—Percentage distribution of lactobacilli in the saliva of the groups examined at Galesburg and at Quincy, classified according to the estimated amount. (Pub. Health Rep. 54: 862, 1939.)

Bacteriologic Findings.—In addition to these clinical observations, quantitative estimations were made of the number of oral lactobacilli in the saliva of 186 children in Galesburg and 209 children at Quincy. The bacteriologic studies were conducted by Dr. Philip Jay (Associate Professor, University of Michigan School of Dentistry) and Passed Assistant Dental Surgeon F. A. Arnold, Jr., United States Public Health Service. The bacteriologic study was purely epidemiologic in that the unit of investigation was a population and not an individual. The group population differences in oral *L. acidophilus* closely reflected the difference in the amount of dental caries. These findings are shown in Table V and Fig. 3.

Saliva Studies.—McClure[39] found that the saliva of the eighty-two Galesburg children showed no differences in amylolytic action from that of the sixty-three Quincy children.

TABLE VI

VARIATION IN THE AMOUNT OF DENTAL CARIES IN 12- TO 14-YEAR-OLD WHITE CHILDREN OF GALESBURG AND QUINCY, ILL.

NUMBER OF DECAYED, MISSING, OR FILLED PERMANENT TEETH	GALESBURG			QUINCY		
	NUMBER OF CHILDREN	PERCENTAGE OF TOTAL EXAMINED	PERCENTAGE OF TOTAL (CUMULATIVE)	NUMBER OF CHILDREN	PERCENTAGE OF TOTAL EXAMINED	PERCENTAGE OF TOTAL (CUMULATIVE)
0	112	35.1	----	12	4.0	----
1	55	17.2	52.3	18	5.9	9.9
2	37	11.6	63.9	16	5.2	15.1
3	34	10.7	74.6	27	8.8	23.9
4	40	12.5	87.1	36	11.8	35.7
5	19	6.0	93.1	34	11.1	46.8
6	9	2.8	95.9	38	12.4	59.2
7	5	1.6	97.5	22	7.2	66.4
8	5	1.6	99.1	33	10.8	77.2
9	3	0.9	100.0	21	6.9	84.1
10				11	3.6	87.7
11				7	2.3	90.0
12				6	2.0	92.0
13				5	1.6	93.6
14				5	1.6	95.2
15				3	1.0	96.2
16				3	1.0	97.2
17				1	0.3	97.5
18				5	1.6	99.1
19				1	0.3	99.4
20 and over				2	0.6	100.0

Total examined: Galesburg, 319; Quincy, 306.

Number of carious permanent teeth per 100 children: Galesburg, 201; Quincy, 633.

Fluoride (F) content of domestic water supply in parts per million: Galesburg, 1.8; Quincy, 0.2.

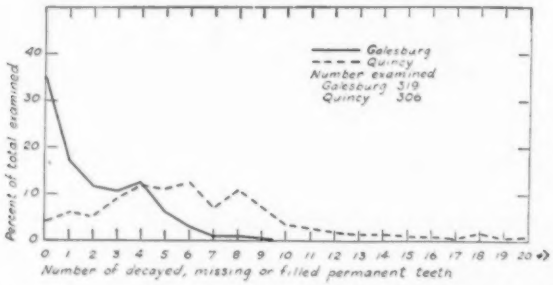

Fig. 4.—Variation in the amount of dental caries in 12- to 14-year-old white children of Galesburg and Quincy.

Chemical Analyses of the Common Water Supplies.—For a detailed report of the mineral composition* of the Galesburg, Monmouth, Macomb,

*For the mineral composition other than fluoride of many of the waters referred to in reference 32, see: Pub. Health Rep. 50: 1719, 1935; 52: 1249, 1937; 54: 212, 1939; and Public Water Supplies of Wisconsin, Wisconsin State Board of Health, July, 1935.

and Quincy water supplies, the reader should refer to the original report[35] of this study.

Gradations in the Force of Dental Caries.—A study of the differences in the amount of dental caries between Galesburg and Quincy would indicate that the vigor or force of the mechanism capable of initiating dental caries is subject to marked communal differences. When general population groups, specific for age and sex, are studied, appreciable differences are observed. But the true magnitude of these differences becomes apparent when the comparisons are made between groups continuously exposed to the risk of the happening in one or the other place. The difference in the intensity of the dental caries mechanism operating in these two communities is so apparent from a study of Table VI and Fig. 4 that little comment seems necessary.

DISCUSSION AND CONCLUSIONS

A considerable quantitative difference in dental caries has been demonstrated epidemiologically among communities in close proximity to one another. A study of the cause or causes of these differences may shed important light upon the etiology and the possible partial control of dental caries.

While on the basis of our present knowledge it appears justifiable to associate the observed results with the presence of fluorides in the common water supply, the possibility should not be overlooked that other elements of comparatively rare occurrence in water or ordinary constituents of drinking water present in unusually large concentrations may directly or through a synergistic action with the fluoride produce the observed effects. All of our studies to date, however, have shown that the use of a domestic water capable of producing even the mildest type of mottled enamel in an appreciable percentage of those continuously exposed is associated with comparatively low amounts of dental caries.

Considering the apparent similarity in the population groups, especially those in Galesburg, Monmouth, Macomb, and Quincy and the methodology followed in the selection of the sample, it is difficult from an epidemiologic standpoint to ascribe these differences to any cause other than the common water supply. It should be pointed out that the present emphasis on the water factor of dental caries is not intended to exclude other factors, which may also be subject to practical control.

Finally, it is apparent that, if future studies continue to confirm the marked communal differences in the amount of dental caries in American children living under comparable conditions, consideration would have to be given to an entirely new reorientation of the problem of dental needs, the future distribution of dental practitioners, the type of dentistry they will be called upon to practice, and other as yet unforeseen developments.

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Round Table Discussion on Abdominal Pain

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Abdominal Pain

Richard M. Smith, M.D., Boston, Mass.

Children who complain of abdominal pain present a problem in diagnosis which confronts the pediatrician on many occasions. To study these children adequately and to evaluate the findings require the utilization of a wide variety of techniques and the exercise of keen clinical judgment. In opening the Round Table today, I want to describe briefly the condition as it is seen in practice and to indicate the direction which it may be most helpful for our discussion to take.

In the infant and young child we all recognize that pain is manifested by crying, restlessness, irritability, and other general symptoms, rather than by a definite complaint. This is necessarily so because, in the infant, speech has not been acquired and because in the young child the ability to localize the source of discomfort is not fully developed. In this group of persons we must proceed in an objective manner. These are not the children about whom we are concerned at the moment.

In the older child pain is recognized as such and can be given vocal expression. Abdominal pain is a common complaint. One may see a patient in whom this symptom is present for the first time. It may be severe or mild, and there may or may not be an associated elevation of temperature, vomiting, diarrhea, frequency of urination, etc. If one is dealing with an acute condition, perhaps an acute surgical abdomen, an immediate decision as to therapeutic procedure is indicated. Some study may be necessary, however, and one must guard against conclusions founded upon inadequate history and examination simply because of the urgency of the situation. These children also are not the ones in whom we are primarily interested now.

The group which we wish to discuss today is comprised of children who, in general, are well, but who have abdominal pain, recurring in attacks extending over a period of months or years. These children may be seen in the first attack or in any one of the subsequent episodes. At the time of the first attack one may find little evidence of the subsequent course and little or no investigation may be undertaken. It is when one obtains a history of repeated attacks that

the picture is of especial interest. The condition is rarely an acute emergency, although at any time it may become so. A most painstaking study is indicated. We recognize that abdominal pain may be the presenting symptom in a great many diseased states, the primary focus of which may be within the abdominal cavity or situated in a remote part of the body. The exact localization of the pain, which has been shown to be an important diagnostic factor in adults, is of relatively little assistance in children. Children usually refer all abdominal pain to the region of the umbilicus, and only rarely before the age of 10 years are they more specific as to the location. One must depend, then, in an investigation of abdominal pain in children upon objective findings and their correlation with the evidence obtained from a careful history. The history may be difficult to evaluate because of the child's indefinite story and the parent's limited powers of observation and narration.

Within the abdominal cavity there are many body systems represented. The major portion of the space is occupied by the gastrointestinal tract. We might consider this body system first. The more common diseases should be given prior consideration, but the rarer conditions cannot be overlooked. Almost every disease of the gastrointestinal tract may cause pain either directly or through extension to or pressure upon other structures. The underlying cause may be mechanical or developmental in origin, as in pyloric stenosis and intestinal obstruction; infectious, as in enteritis, appendicitis, and colitis; functional, as in spastic colon and indigestion; or undetermined, as in ulcer and neoplasms. Emotional factors may play an important role. To determine which one, if any, of these conditions is present, one needs the supplementary information obtained from many laboratory investigations. Roentgenograms of the abdomen, skull, long bones, chest, and sinuses, and of the gastrointestinal tract with ingestion of barium, may be necessary. Blood studies of the red and white cells and of the platelets and urine examinations should be made in every case. Often chemical determinations of the blood and visualization of the urinary tract by intravenous or retrograde pyelography will be employed. Tuberculin tests and agglutinations and other special procedures will be indicated in many cases.

In addition to the gastrointestinal tract, there are within the abdominal cavity the liver, spleen, pancreas, genitourinary tract, adrenals, blood vessels, lymph glands, and the peritoneum. Not all diseases of all of these structures cause intermittent attacks of pain, but in some disease of each, pain is an important symptom. Infection is the etiological factor in connection with many of these diseases, especially those of the kidneys, lymph glands, and peritoneum. New growths in children, although not commonly the cause of recurring attacks of pain, cannot be left out of consideration, especially ovarian cysts and metastases of tumors to lymph glands. The disease causing pain may be primary in any of the abdominal organs or secondary to disease elsewhere in the body. General systemic diseases, such as purpura and allergy, may have abdominal manifestations which cause pain. A review of the diseases of all the abdominal tissues is necessary.

The most confusing cases of abdominal pain are those in which there are no lesions in the abdominal cavity. Diseases in various parts of the body may, under certain circumstances, cause no pain at the site of the lesion, but pain is referred to the abdomen. Intracranial disease, rheumatic fever, disease of the spine, diabetic coma, lead poisoning, and respiratory diseases are illustrations. The consideration of these conditions involves a knowledge of nerve distribution, especially in the abdominal cavity, and some understanding of the autonomic nervous system.

In order that we may refresh our memories concerning the nerve supply of the abdominal organs and structure and the working of the autonomic nervous system, Dr. Snedeker will review briefly the pertinent facts relating to these subjects.

Some Neurologic Aspects of Abdominal Pain

Lendon Snedeker, M.D., Boston, Mass.

I have been asked to discuss briefly some of the neurologic aspects of abdominal pain. Abdominal pain is not only a frequent indication of disease, but is often difficult to evaluate. As Ryle has pointed out, there is a dearth of knowledge about this very important symptom, although recent advances, especially in the field of sympathetic surgery, have been enlightening. Pain in childhood, for obvious reasons, has not been a very popular subject for study.

What produces pain in the viscera? This question puzzled Lennander, for he showed by experiments during abdominal operations that the viscera were insensitive to cutting, pinching, burning, and all customarily painful stimuli. He concluded that sensation resided in the parietal peritoneum, which was known to be richly supplied with cerebrospinal nerves. Subsequent work has shown that the viscera are actually the seat of painful sensations, but that the requisite stimuli differ from those we should ordinarily expect. Stretching of the capsule of such solid viscera as the liver, spleen, and kidneys is the appropriate stimulus. In the case of hollow viscera, however, contraction of the muscular coat produces the pain. Such a state of muscular tension may be due to sudden distention of the viscus or to failure of muscle to relax in the presence of increasing intravisceral pressure. Usually the more quickly tension is produced, the more acutely will pain be felt. Local irritation of the peritoneum is another adequate stimulus, whether it is produced mechanically or by inflammation. The work of Capps and Coleman has shown that mechanical stimulation of the anterior surface of the peritoneum produces pain which is accurately localized on the outer abdominal wall with an error of no more than one inch.

The end organs for pain perception are of several kinds. For example, the mesentery contains large numbers of pacinian corpuscles which are sensitive to mechanical deformation and which, therefore, serve for the perception of deep pressure and possibly for vibration. Most painful sensations are, however, perceived by free nerve endings in the viscera, as is the case with ordinary cerebrospinal nerves. Afferent impulses are transmitted from these end organs by fibers which pass through the sympathetic ganglia on either side of the spinal cord and end in the gray matter of the cord after passing through the posterior nerve roots. The pain sensations then either pass by way of new neurones up the spinothalamic tracts to the brain or are translated into reflex motor responses by motor nerve fibers. These pass out of the anterior nerve roots to the sympathetic ganglia. Secondary or post-ganglionic fibers originate in these ganglia and make their way to the sympathetic plexuses about the viscera and thence to individual muscle fibers.

Since the functions of our internal organs are more apparent than their sensibility, we often think of them solely in terms of motor impulses. It should be emphasized that a large part of the nerve supply to our viscera is a sensory one. For example, more than half of the fibers in the splanchnic nerve serve this purpose.

In 1863 John Hilton pointed out the significance of external pain in relation to internal disease. Ross, Head, and MacKenzie went on to demonstrate that disease in a viscus tended to be appreciated as a localized area of pain on the surface of the body. MacKenzie was, however, puzzled by the fact that, although the affected viscus might be constantly shifting its position, the painful area remained fixed. Furthermore, in the case of lesions of the gastrointestinal tract, pain was usually felt in the midline. Hertz explained this on the basis of what he called "average localization"; that is, although the viscus was constantly shifting, the body came to perceive the pain in one fixed place. Furthermore, it

was found that in addition to pain there were often skin areas which were unusually sensitive to touch. These were called zones of "hyperesthesia" or "hyperalgesia," depending upon whether the sensation produced by stroking or pinching was one of increased sensibility or of actual pain. Head used these areas of hyperesthesia to map out the sensory distribution of the various spinal segments and secondarily to deduce the sympathetic nerve supply of the viscera.

To explain these phenomena Ross initiated and MacKenzie elaborated the concept of "referred pain." According to this theory, the afferent impulses from a diseased viscus produced an "irritable focus" in the spinal cord and led to the secondary stimulation of cerebrospinal nerve fibers supplying the exterior of the body. The perception of pain was, therefore, "referred" to the skin, in which case a "viscerosensory" reflex had been produced; if muscle contraction occurred, a "visceromotor" reflex had occurred. By this hypothesis MacKenzie explained the epigastric pain of early appendicitis and the later spasm of the rectus muscle. He also pointed out the classical examples of the radiation of pain to distant parts and gave a reasonable explanation as to why cardiac pain was referred down the inside of the arm, gall bladder pain to the scapula, and the pain of ureteral colic to the loin and groin.

It should be remembered that the pain produced by palpation directly over a viscus is not really "visceral," but is "referred," pain. For instance, although a gastric ulcer is insensible to direct palpation, pain is appreciated externally on deep pressure. This may be an instance where the pacinian corpuscles are functioning. True visceral pain is more likely to be vague and ill defined like soreness or a sense of local discomfort.

This theory explains a few other clinical phenomena. Irritation of the outer margins of the diaphragmatic peritoneum causes pain over the distribution of the lower six intercostal nerves, that is, over the lower chest and upper abdominal wall. Stimulation of the central portion, however, produces pain over the ridge of the trapezius muscle, owing to the common innervation of these structures by the phrenic nerve. It happens that the central portion of the diaphragm is derived from cervical myotomes. The vagus nerve supplies the gastrointestinal canal as well as some of the structures in the neck. For this reason intestinal colic may be accompanied by hoarseness, or, conversely, it is theoretically possible that inflammation of the throat would be perceived in part as abdominal pain. Excessive stimulation of the sensory part of the vagus may produce facial neuralgia and alter the sensitivity of the upper portions of the alimentary mucosa. All viscera with a vagal supply may refer stimuli to the fifth cranial nerve and cause pain in some of its peripheral branches. Occasionally abdominal pain accompanies pneumonia. Although the lungs are insensitive, secondary irritation of the parietal pleura and the related intercostal nerves will, as in the case of the diaphragm, cause pain over the lower chest and upper abdomen. Abdominal pain may accompany certain brain lesions. The work of Penfield and others suggests that there is a sensory autonomic representation for the gastrointestinal tract in the cortex. This accounts for the abdominal pain sometimes occurring in epilepsy and migraine. Cushing has observed a number of patients who were operated upon for brain tumors and who subsequently developed ulcers of the stomach or small intestine. This appears to be further evidence that there is some connection between the brain and the gastrointestinal mucosa. The probable course of the nerve pathway is from cortex to hypothalamus to red nucleus to substantia nigra and then to the gastrointestinal tract by way of the vagus nerve.

Both anatomic proximity and a common innervation account for the fact that disease in one part of the gastrointestinal tract may produce symptoms in other parts. Persons with anal lesions such as hemorrhoids may show the symptoms of an

"irritable colon" or gastric ulcer. Experimentally it has been shown that stimulation of the anal region in dogs will alter the contraction waves in regions as far removed as the duodenum. Similarly, renal disease, cardiac disease, and affections of the liver may cause abdominal symptoms. In the case of renal pathology one should remember how intimately the kidneys and duodenum are related and how traction on the renal ligaments might produce secondary effects in the intestinal tract. The common renal sources for gastrointestinal symptoms are ureteral stricture, hydronephrosis, movable kidney, and renal stone.

A number of men have tried to estimate the value of hyperesthesia of the skin in the diagnosis of abdominal disease. Sherren found it to be present in 40 out of 124 patients with appendicitis. Livingston has noted cutaneous hyperesthesia and hyperalgesia in 86 per cent of 400 consecutive cases of appendicitis. Both of them agree that this sign is absent in cases with a gangrenous or ruptured appendix, that is, in situations where intravisceral tension had been spontaneously reduced. For abdominal pain in general, Cope finds hyperesthesia in one-half of his patients, and in appendicitis in 59 per cent of them. Other authors have reported this finding about one-third of the time, and Cope explains this on the basis that they took actual pain (hyperalgesia) rather than increased sensibility (hyperesthesia) as their criterion. A number of observers doubt the value of these findings, among them Robinson, Morley, and Boland; but the balance of the evidence is in favor of their validity when present. Undoubtedly they are often perceptible if we will only take the trouble to look for them.

TABLE I

SENSORY INNERVATION OF THE VISCERA

ORGAN	AREAS OF PAIN REFERRAL	NERVE SUPPLY
Heart	Precordium and inner arm	T1-T5
Lung	No pain till parietal pleura and intercostals involved	----
Diaphragm	Lower chest wall and upper abdomen; central portion to trapezius ridge	T6-T12 Phrenic nerve
Esophagus	Substernal region	T5-T6
Liver and gall bladder	Right upper quadrant; right scapular region	T7-T8
Stomach	Epigastric region	T7-T8
Small intestine	Umbilical region	T9-T10
Appendix	Epigastrium; later the right lower quadrant	T10
Large intestine	Suprapubic region	T12-L2
Kidney	Loin and groin	T12-L2
Ureter	Loin and groin	L1-L4
Bladder	Suprapubic region	T10-L4
Uterus	Suprapubic region and lower back	T12-L2

The observations of Head on the segmental nerve supply of the viscera have been confirmed and modified through denervation experiments and work with sympathectomized patients. The sensory supply to the viscera is now fairly well known and is summarized in Table I taken largely from White. A review of this table shows that for every section of the gastrointestinal tract there is at least one organ with a similar innervation. This perhaps explains why gastrointestinal symptoms are so often a concomitant of abdominal disease whether or not the gastrointestinal tract is the seat of the lesion. It also creates obvious diagnostic difficulties in the use of areas of hyperesthesia for diagnosis. It should be noted, however, that in almost every case, pain from viscera, other than the gastrointestinal tract, shows a greater tendency to radiate and be referred. For example, the gall bladder innervation is identical with that for the stomach,

but gall bladder pain is apt to be referred to the region of the scapula. It is unusual for pain originating in the gastrointestinal tract to be referred, although MacKenzie mentions pain and tenderness over the dorsal spines. Certain other factors must be considered in the evaluation of pain.

When pain has lasted for long periods of time, there is a tendency for its referral to be augmented and for the areas of hyperesthesia to increase. The dependability of these signs is thereby reduced considerably. The patient's threshold for pain has been lowered, and trivial causes produce impressive effects. Patients with acute pain are, therefore, obviously more profitably seen early. Even if the affected organ has already been removed surgically, the patient may feel the old pain for some time after operation. Furthermore, people differ in their capacity to feel pain. Libman has investigated the sensitivity of various persons to such a stimulus as the pressure on the mastoid, and he finds they fall into hyposensitive and sensitive groups. He stresses the importance of not underestimating symptoms in the hyposensitive person and finds that these patients feel less or none of the pain of a given disease. They are more likely to refer painful impressions to the side opposite the lesion and to present more of the reflex and referred manifestations of the syndrome. He, therefore, considers Head's areas more significant in the hyposensitive person.

So far we have discussed the nerve pathways for pain and its localization on the surface of the body. There are certain other interesting phenomena associated with abdominal pain. For instance, in addition to referred pain or areas of hyperesthesia, there may occur erection of body hair, altered vasomotor responses in the skin, and even, in chronic cases, muscle atrophy. Pottenger mentions such atrophy affecting the neck muscles in prolonged cases of tuberculosis. Vomiting is controlled through the derivatives of the seventh, ninth, tenth, and eleventh cranial nerves, and both the vagus and the splanchnic nerves carry reflex stimuli which lead to vomiting. Another interesting phenomenon is the so-called "flexion reflex" which is a mass reflex brought on by a variety of harmful stimuli. In cats distention of the stomach with air or a mixture of mustard in oil is followed by flexion of the trunk and extremities. Spinal man shows this same reflex with a full bladder. In the intact person, flexion can be produced by sudden distention of the gall bladder or intestines or by stimulation of the peritoneum. Two purposes are served by this reflex: first, the body is immobilized; and second, the omentum is displaced downward so that it covers the anterior surface of the abdominal viscera and favors the walling-off of infection.

Let us consider the measures used for the relief of abdominal pain in terms of the neurologic mechanisms involved. Morphia is our most effective narcotic and acts on the higher centers. For this reason its use in abdominal pain is a potential danger, inasmuch as all sensations tend to be dulled and useful diagnostic signs obliterated. The action of atropine is more peripheral, for this drug produces parasympathetic (i.e., vagal) paralysis and diminishes peristalsis. Relaxation of the cardiac and pyloric sphincters also occurs. In cases where pain is not acute and severe, it may be an effective drug. Except for the relief afforded by such medical measures as catheterization of the bladder or the natural loss of pain when a stone is passed, surgery is usually required for the relief of acute abdominal pain dependent upon any sudden increase in intravisceral tension. Of late the surgeon has been able to relieve other visceral pains through his knowledge of the anatomy of the autonomic (sympathetic) nervous system. Alcohol nerve-block may be used for temporary effects and sympathectomy for permanent relief. Neither of these procedures, of course, lends itself to diagnostic use. You are already acquainted with the results secured in cases of intractable

cardiac pain and the often excruciating pain experienced in arterial disease affecting the extremities. Such surgical procedures have been of therapeutic value as well as of service in demonstrating experimentally the nervous pathways for pain. Liver pain can be relieved by splanchnic nerve-block and bladder pain through sympathetic denervation. Meigs has had some success with the relief of dysmenorrhea by presacral neurectomy. Recent experiments by White show that ureteral pain can be relieved by stripping the nerve supply off the ureter. Unfortunately, most of these measures are adapted to chronic diseases which are rarely encountered by the pediatrician.

As Pottenger has so ably pointed out, the difficulties encountered in the clinical study of visceral pain are: first, the individual variations in reaction to the same stimulus; second, the patient's inability to describe accurately his symptoms; and third, the physician's inability to comprehend and interpret the symptoms. The important symptoms are not solely those of an uncomfortable or painful character, but also the disordered functions which a careful search will usually show to be connected with those sensations. No one can accuse the pediatrician of having chosen the most cooperative and self-expressive patient for investigation, and it therefore behooves him especially to consider this functional aspect. His only consolation is that he will not receive from his patient a long and complicated history full of false diagnostic leads. In view of this discouraging state of affairs, it is up to him to discover in the patient every possible clue to the localization of the disease process confronting him. He will need some knowledge of visceral innervation if he is to be successful in his efforts.

Borden S. Veeder, M.D., St. Louis, Mo.

Fortunately we are to discuss only the chronic recurrent type of abdominal pain in older children, as a discussion of all types and ages would require a text. I have written down an incomplete schema of the chief causes simply to give direction to the discussion.

A. Gastrointestinal tract
   - Chronic digestive disturbance (including allergy)
   - Colitis
   - Chronic appendicitis
   - Mesenteric lymphadenitis
   - Anomalies

B. Lesions of genitourinary tract
   - e.g., Calculi, Intermittent hydronephrosis

C. Uncommon conditions
   - e.g., Ovarian cyst, Gall bladder disease, rheumatism, purpura, etc.

In the examination I would first of all emphasize the history. This is so important because frequently the physician never sees the child during an attack of the pain. The history, of course, is apt to be indefinite, as is the pain. Going over the story again and again often gives new points. For example, a few months ago a child came into the hospital because of recurrent attacks of abdominal pain observed by several physicians. A diagnosis of appendicitis had been made and the appendix taken out, but the pain continued. An alert house officer in taking the history learned the attacks were followed by copious urination. With this clue, inside of forty-eight hours a definite diagnosis of intermittent hydronephrosis was made by roentgenograms, and the pain was relieved by a second operation.

The points to be considered in the history are these:

Duration of pain

Character

- Intensity
- Sharp or dull (distress)
- Continuous or intermittent; long intervals or short intervals

Location

- Position in abdomen—
  quadrant, flanks, umbilical
- Fixed or changing
- Direction or radiation

Association with

- Fever
- Vomiting
- Diarrhea
- Constipation
- Certain, or unusual, foods
- Urination
- Menstruation
- Exercise

What, if anything, gives or brings about relief from pain?

Dietetic habits of the child

We must realize, of course, that pain is a very vague indefinite thing—what is a little pain to one is severe pain to another. Great caution must be exercised in evaluating the degree and intensity of the pain as given in the history. The location is apt to be vague in younger children, and consideration must be given to attention to some point having emphasized location. The vague but important characterization of "neurotic" as regards both the parent and child must be taken into consideration in respect to the intensity of pain. In older children the question of localization and radiation may be a great deal of help.

Association with other findings, such as vomiting, constipation, or specific foods, may be of utmost importance, and, as far as these points are concerned, the only source of information. I recall the case of a child, before the days of "allergy," in which recurrent attacks of pain were found to occur only after visits to one particular friend's house; the pain was found due eventually to the eating of red-hots on these visits.

What relieves the pain may be of great help in determining its origin, as with urination mentioned above, vomiting, an enema, etc.

As far as the examination goes we presuppose a general examination to rule out causes such as rheumatism, Banti's disease, etc. I consider the general habitus of the child, its nutritional condition, as important as the manual examination of the abdomen, which usually offers little. Perhaps at times localized masses or tenderness may be found, but as a rule these are infrequent findings. Rectal examination rarely gives help.

In addition to the routine blood and urine examination, we must turn to roentgenology in many cases. My own feeling is that, with few definite exceptions, such as anomalies, x-ray examination of the gastrointestinal tract gives little help, but it must be used frequently. Only exceptionally in the case of children is it of help in chronic appendicitis, granted such a condition exists. Gastrointestinal roentgenology in my experience confirms, rather than makes, a diagnosis.

Urologic roentgenology is more helpful when lesions of the genitourinary tract are present. Such examination requires careful technique to be of help.

With a condition or complaint due to so many causes, and with so little specific help available, it is no wonder many cases require long and repeated observation before a diagnosis can be made or relief obtained. Surgery, I feel, is a last resort unless specific definite information is at hand indicating surgical intervention.

In the physical examination we presuppose that the child has a complete general examination, and hence our discussion is limited to the abdomen alone. The points of most importance are these:

Habitus and general nutritional condition of the child
Palpation of abdomen (Difficulties due to fear, resistance, uncertainty, and lack of cooperation)
Tenderness
Masses or deep resistance
Muscle guarding
Rectal examination

The habitus or nutritional status is important. In a well-nourished child the pain is apt to be functional, due to excessive gas. When there is a deep-seated lesion, such as hydronephrosis or a chronic infection, as a rule it shows clearly in the nutritional condition.

Palpation may or may not be of aid. When masses or persistent localized tenderness are present, we have a most important finding. But these findings are exceptional. Rectal examination is of little value except in the rare cases in which a pelvic mass is present.

Naturally certain routine laboratory examinations must be made, such as blood and urine (catheterized specimen in girls) tests.

To these are added certain special examinations, if indicated, as the tuberculin test, roentgenologic examination (flat, gastrointestinal, and urologic), proctoscopic examination, and stool examinations.

As regards roentgenograms, the flat plate will show little besides the kidney position and stones. Gastrointestinal examinations, in my experience, are of relatively little help, that is, the x-ray examination confirms, rather than gives, a diagnosis.

As a rule, urologic roentgenograms are much more valuable as an aid in diagnosis.

DISCUSSION

DR. A. J. BELL, CINCINNATI.—It has been suggested that in cases in which the trouble is still within the appendix a different set of nerves is involved than when it reaches the peritoneal wall; and that early the pain is intermittent in character and referred to the region of the umbilicus, and later, when the peritoneal wall becomes involved, typical tenderness and rebound pain may be elicited. Is there any basis for this idea?

DR. SNEDEKER.—Pain in the upper region is the pain Capps and Coleman produced by irritating the peritoneal surface. Chester Jones has shown that distention of the intestinal tract produces pain. The early pain in appendicitis is due to muscular contractions.

DR. MARTIN.—I would like to queston the somatic reaction. We must consider the neurotic phase in children complaining of abdominal pain. The history is very important. Some children have pain only on school days. It is also important to make careful urologic study; we recently saw a patient in whom careful history

taking revealed that the pain would cease after emptying of the bladder. Studies, I think, are of value in the tall thin type of child in whom there is often ptosis of the colon and stomach.

CHAIRMAN SMITH.—We have all experienced these cases due to neurosis. This diagnosis should only be made by exclusion, and I think it is the very last thing to consider.

DR. L. F. HILL, DES MOINES.—What relation has a great amount of milk intake and constipation to abdominal pain? It has been my experience that if milk is stopped the pain usually disappears. Is this an allergic phenomenon or indigestion?

DR. VEEDER.—I do not think this is an allergy. It is more likely to be due to the general type of the diet. However, occasionally we find an allergy to milk.

DR. P. F. BARBOUR, LOUISVILLE.—I think we should always consider kidney lesions, particularly if the pain occurs following exercise. The presence or absence of peristaltic waves is of great significance. No peristaltic movements are elicited in acute abdominal conditions. Sylvester of Boston reported that, out of 1,000 patients operated upon for abdominal conditions, the pain was found to be referred in 85 per cent of the cases. Intolerance to fat often induces pain in the abdomen of infants. Sylvester also listed about sixty-nine diseases which may cause pain in the abdomen.

CHAIRMAN SMITH.—I think we should devise some new method for the further study of cases of this kind.

DR. A. G. JACOBS, MEMPHIS.—I would like to ask about the value of pain in pylorospasm; also the value of x-rays.

DR. VEEDER.—Undoubtedly there is pain in pyloric stenosis. Possibly the only expression of pain in the infant is that of crying.

CHAIRMAN SMITH.—There is a group of infants and older children with recurrent attacks of abdominal pains which are very difficult to classify. We are in the rabit of calling these "abdominal pain, cause unknown; referred for further study."

DR. R. COHN, TOLEDO.—Many babies with pyloric stenosis vomit without crying.

DR. VEEDER.—One person's guess is as good as another's.

DR. COHN.—We should also consider referred pain from the respiratory infection, which often gives rise to a diagnosis of appendicitis. I saw a child lately who, with each respirafory infection, would have repeated attacks of abdominal pain, and with the last attack he came down with measles.

CHAIRMAN SMITH.—There is no question about the fact that upper respiratory infection will cause abdominal pain.

DR. O. E. BARBOUR, PEORIA.—Will you discuss mesenteric adenitis?

CHAIRMAN SMITH.—With pain in the right lower quadrant, no one can make a differential diagnosis. Left upper quadrant mesenteric adenitis is more common and is often seen with recurrent attacks of sinusitis.

DR. HUGHES KENNEDY, JR., BIRMINGHAM.—Pains occurring soon after eating are relieved in many cases by atropine, but in some patients this gives no relief. What would you do in such a case?

DR. VEEDER.—We have often used atropine, but if the pain does not come on in relation to the taking of food, there is usually no effect by the drug.

CHAIRMAN SMITH.—Barium enema is more likely to give further inflammation in atony of the large bowel.

DR. COHN.—Do you consider colic a neurosis?

DR. VEEDER.—I do not.

DR. SNEDEKER.—Some children may be more aware of peristaltic waves than others.

DR. COHN.—May some of these pains in a child 6 or 7 years old be caused by hunger contractions?

CHAIRMAN SMITH.—Consciousness of peristaltic contractions may be more acute at some times than at others.

DR. RAND, CINCINNATI.—Do you feel that enemas or cathartics should be used in perityphlitis?

DR. VEEDER.—The chronic enema habit is bad, but enema usually relieves the pain.

DR. RAND.—I meant that if you see a child with pain and if you find a boggy cecum, would you give enemas or cathartics?

DR. VEEDER.—Enemas, but no cathartics.

DR. M. F. OSTERLIN, TRAVERSE CITY, MICH.—What is the cause of pain in the left upper quadrant?

DR. VEEDER.—This is usually gas, and is very commonly found. It often is referred to the heart.

CHAIRMAN SMITH.—We must always keep in mind the interrelationship of various organs within the abdominal cavity.

DR. J. H. GERSTLEY, CHICAGO.—It is true that many upper respiratory infections cause pain referable to the abdomen, but we must consider the possibility of true appendicitis with an upper respiratory infection. I think many such cases are overlooked.

DR. A. J. CRAMER, BUFFALO.—In 150 cases operated upon for appendicitis, 72 per cent had complete recovery, 10 per cent were benefited, and the balance were a total failure so far as relief of abdominal pain was concerned.

DR. VEEDER.—In ear infections and upper respiratory infections I wonder if the patient has true pain in the abdomen or if it is more a feeling of sickness and nausea.

DR. BARBOUR.—Would you discuss the pleurodynia?

DR. SNEDEKER.—I suppose it is a referred pain from the intercostal nerves innervating the outer border of the diaphragm.

CHAIRMAN SMITH.—It may possibly be similar to the pain of herpes zoster.

DR. N. D. GANNON, ERIE, PA.—In many of my cases of abdominal pain the children have had cramplike intermittent pain, persistent vomiting with normal temperature, later followed by diarrhea and light-colored stools and mucus.

CHAIRMAN SMITH.—I think these cases come in the group of intestinal infections with hyperperistalsis.

DR. COHN.—The pain in Meckel's diverticulum often simulates the pain of gastric ulcer.

CHAIRMAN SMITH.—The pain is often of that nature, but careful x-ray studies may give the diagnosis.

DR. R. D. HOSTETTER, DAYTON.—I have found it of value to have the mother write down the diet given to the child over a period of one week. This has proved to be important in making a diagnosis.

DR. VEEDER.—We recently saw a child with negative physical findings, whose diet had apparently been normal and in whom all tests were negative. He had pain which persisted and recurred. Suddenly the mother discovered that the pain occurred after the visit to a certain home. The diet was found to be average in that home, but the child had eaten red-hots and candy, to which he was sensitive.

DR. KENNEDY.—I have found children who tolerated strained foods, and if the foods were not strained, they often developed fever, nausea, and vomiting. Is this fever due to stimulation of the sympathetic nervous system?

CHAIRMAN SMITH.—We all have experienced high fever due to this type of foreign body. I think it is due to stimulation of the sympathetic nervous system.

DISCUSSION ON SATURDAY MORNING

November 18, 1939

DR. J. S. WALL, WASHINGTON, D. C.—The physiologic background of the child should always be emphasized. The child always takes his abdomen as a defense mechanism. Milk is a common cause of abdominal pain.

CHAIRMAN SMITH.—One must always consider the emotional factors in pain. However, beware of such a diagnosis.

DR. L. D. HOPPE, JR., ATLANTA, pointed out the differential diagnosis between lymphadenitis and chronic appendicitis.

DR. VEEDER.—Differential diagnosis of the above conditions often is difficult. Lymphadenitis often follows acute infections. Likewise, it is less stormy in its course. There is less abdominal spasm. One may have to operate to rule out appendicitis. The blood picture may help some in showing the blood shift in the case of appendicitis.

DR. THEODORE RUSSELL, BATTLE CREEK.—What about the diagnosis of spondylitis or spinal pain? Is it arthritis?

CHAIRMAN SMITH.—One should always rule out spinal disease. Especially rule out recurrent spinal disease. Always keep in mind a mild Pott's disease.

DR. SNEDEKER.—One may also get patients with pains referred to spine. Your case may be pleurodynia; it may be segmental neuralgia. These cases may or may not develop herpes. These are probably virus infections.

DR. VEEDER.—We have seen an epidemic of pleurodynia. These children usually are quiet until they move or pressure is made during examination.

DR. SCHLESSINGER, DENVER.—Rheumatic fever may be a cause of abdominal pain.

CHAIRMAN SMITH.—Abdominal pain from rheumatic fever is not usual, but it is an occasional symptom.

DR. WALL.—Can we discuss chronic appendicitis? Should it be a diagnosis?

DR. VEEDER.—I believe there is such a condition, but time will not permit a discussion of this subject.

CHAIRMAN SMITH.—Occasionally pinworm will be a cause of abdominal pain. It is involvement of the appendices.

DR. H. B. METTEL, INDIANAPOLIS.—Routine sections of appendices of post-mortem cases in the Riley Hospital, Indianapolis, show a great many appendices invaded by a large number of pinworms. This symptom is probably much more common than we have heretofore thought.

DR. J. E. DYSON, DES MOINES.—I once saw a case in which round worm was a cause of appendicitis. One should also think of seasons in July, such as the Fourth of July, hot dogs, etc.

DR. RUSSELL.—One should not forget spasm of the colon or the pain commonly seen in childhood after exercise.

CHAIRMAN SMITH.—Many times gastrointestinal x-rays do not help, but when they do give information, they are of great help. A gastrointestinal series should always include a barium enema.

DR. HOPPE.—A skin test of allergic cases does not give much information in the gastrointestinal type of allergy.

DR. METTEL.—Another cause of abdominal pain difficult to diagnose is in that group of young girls who are beginning their menstrual periods. It is often difficult to decide if these young girls do or do not have a subacute appendicitis. This is especially difficult when we are seeing children in the clinic who are coming in from rural areas and cannot be seen during their acute attacks.

DR. M. B. BROOKS, LOS ANGELES.—Children who are forced to eat or who have poor eating habits are usually the ones who often show vague abdominal pain.

CHAIRMAN SMITH.—Three principal factors involved in pain may be divided into the following classifications: (1) food; (2) allergy; and (3) emotional causes.

DR. MARVIN ISRAEL, BUFFALO.—How would one diagnose rotation of the bowel?

CHAIRMAN SMITH.—Use a barium enema.

DR. VEEDER.—One should always think of the general picture of the nutrition of the child in making a decision of causes of abdominal pain.

DR. D. L. SMITH, JR., SPARTANBURG, S. C.—A "stitch" in the side may be a cause of abdominal pain. This may be caused by a cardiac condition or local spasm of intestine. It is usually relieved by having the patient throw a stone or rest.

DR. WALL.—This condition may be a tension on the abdomen.

DR. S. D. MILLS, WESTFIELD, N. J.—How can you interpret a report of redundancy of the colon?

CHAIRMAN SMITH.—This may be a mechanical change in the function, as Dr. Wall has just said. These children who present recurrent abdominal pain need a prolonged study in order to make a certain diagnosis. Very careful study of the history and frequent examinations with constant review will finally eliminate the condition. The causes of abdominal pain are numerous, and we should not be satisfied until we have exhausted all possible means and have always considered the pathologic conditions outside of the abdominal cavity. In many cases we may be able to make a definite diagnosis or find a definite cause. Pain cannot be solved in a single examination or sitting. It is often necessary to repeat history and physical examinations of children with recurrent abdominal pain.

MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting was called to order by President Joseph B. Bilderback at 2:30 P.M., Sunday, May 5, 1940, at the Orrington Hotel, Evanston, Ill. Those present were:

Dr. Joseph B. Bilderback, President
Dr. Richard M. Smith, Vice-President
Dr. Clifford G. Grulee, Secretary-Treasurer
Dr. Stanley Nichols, Regional Chairman of Region I
Dr. A. Graeme Mitchell, Regional Chairman of Region III
Dr. Edward B. Shaw, Regional Chairman of Region IV

Associate Regional Chairmen

Dr. Lewis Webb Hill
Dr. Hugh Leslie Moore
Dr. Edgar E. Martmer
Dr. Hugh Berkley

The following applicants were elected to membership:

Region I

Dr. John W. Canaday, Glens Falls, N. Y.
Dr. Robert D. M. Cunningham, Stamford, Conn.
Dr. Ralph W. Daffinee, Melrose, Mass.
Dr. Wilbur J. Fisher, Buffalo, N. Y.
Dr. Harry H. Gordon, New York, N. Y.
Dr. Mildred W. Jackson, Oyster Bay, N. Y.
Dr. A. Wilmot Jacobsen, Buffalo, N. Y.
Dr. Harold Lipschitz, Brooklyn, N. Y.
Dr. Merritt B. Low, Greenfield, Mass.
Dr. William R. Phillips, Elmira, N. Y.
Dr. Edwin W. Rodenheiser, Upper Darby, Pa.
Dr. Joseph Schwartzman, Brooklyn, N. Y.
Dr. Russell B. Scobie, Newburgh, N. Y.
Dr. Clement A. Smith, Boston, Mass.
Dr. Martin L. Stein, Brooklyn, N. Y.

Region II

Dr. Harry E. Baldock, Charleston, W. Va.
Dr. Jack Basman, Charleston, W. Va.
Dr. J. Gilbert Eblen, Knoxville, Tenn.
Dr. Thomas G. Folsom, Huntington, W. Va.
Dr. George T. O'Byrne, Tyler, Texas
Dr. Charles E. Ward, Jackson, Miss.

Region III

Dr. Ralph E. Dyson, Minot, N. D.
Dr. George Eisenberg, Chicago, Ill.
Dr. Seymour Fisher, Normal, Ill.
Dr. H. Sidney Heersma, Kalamazoo, Mich.

Dr. Stanley V. Laub, Detroit, Mich.
Dr. Matthew Lewison, Chicago, Ill.
Dr. George C. Malley, Zanesville, Ohio
Dr. Thomas Myers, St. Paul, Minn.
Dr. Harold B. Rothbart, Detroit, Mich.
Dr. Maurice A. Spalding, Milwaukee, Wis.
Dr. Ralph H. Verploeg, Denver, Colo.
Dr. Warren E. Wheeler, Lansing, Mich.

Region IV

Dr. Ralph N. Barlow, Logan, Utah

Dr. Charles K. Johnson of Burlington, Vt., was elected to Emeritus Fellowship.
The resignation of Dr. F. J. Schatz of St. Cloud, Minn., was accepted.
The following were elected to Honorary Fellowship:

Dr. Robert Debré, Paris, France
Dr. Ernst Freudenberg, Basel, Switzerland
Dr. Leonard G. Parsons, Birmingham, England
Dr. Arvid Wallgren, Upsala, Sweden

The treasurer's report and budget were discussed and approved.

It was decided that the Canadian dues should be accepted at par as has been done in the past.

Dr. Edgar E. Martmer, Detroit, Mich., was appointed assistant to the secretary at a salary of $100 a month, and travelling expenses.

Dr. Bert I. Beverly, chairman of the Committee on Mental Health, was present to discuss the matter of a film of the first three years of life. It was moved and carried, with one dissenting vote, that the Committee on Mental Health be allowed to proceed with negotiations for the film, but that the same rules and regulations would have to be followed as with our previous film, final negotiations to be approved by the Executive Board.

It was moved and carried that the historian be included as an officer of the Academy, but that he shall not be a member of the Executive Board.

Dr. Edgar E. Martmer, chairman of the Program Committee, discussed arrangements for the annual meeting, which is to be held at the Hotel Peabody, Memphis, Tenn., November 18-20. Since it was deemed advisable to have some person other than the secretary of the Academy, look after the scientific and educational exhibits, it was suggested that Dr. Thomas Mitchell of Memphis be asked to do so since he has had a great deal of experience with regard to such exhibits. A motion was made and carried that the tickets for the round table discussions be surrendered one hour before the time of the discussion in question. It was also suggested to dispense with the panel discussions for the coming meeting.

To the Committee on Legislation were referred some suggested changes in the constitution and by-laws. Since additional changes were suggested at the meeting of the Executive Board, these have all been referred again to the Committee on Legislation to formulate, so that they can be submitted to the members in time for action at the November meeting.

The report of our publicity expert was given by Mr. Lawrence H. Selz. He told us that his clipping bureau has sent to him 328 clippings from the Edgewater Park and Washington meetings alone. These were scattered in publications all through the south and east. There was also an article in the April 15 issue

of *Newsweek*. He commented upon the accuracy of the information obtained in the clippings and said that this was largely due to the cooperation of the Academy members and the reporting of the material. Twenty-one separate stories were released through organized facilities such as the Associated Press, United Press, North American Newspaper Alliance, and Science Service. In addition to this, an extensive radio program was carried on, with free radio time for two hours and twenty-five minutes at these two meetings. Some progress has been made apparently with magazines of larger circulation, for some of them are asking for articles.

The Committee on Central and South American Scholarships reported that at the time they had four scholarships assured.*

The Committee on Child Health Relations reported the advances which it has made in extending its activities throughout the country through the various state committees and its cooperation with the Children's Bureau in Washington. Emphasis now is being placed upon the quality of pediatric services. Definite contact with the state health departments is being made through the agency of the state committees. The report was accepted as read.

It was decided to discontinue the Committee on Clinical Investigation and Scientific Research.

Aside from the usual activities which are so well known to the members of the Academy, the Committee on Contact Infections has been interested in having articles published in various magazines, among them the *Advance*, a religious magazine, *Parents' Magazine*, and the *Journal of the American Medical Association*. The committee has also been working on a moving picture, although the proposition has not yet been definitely determined upon. The report was accepted as read.

The report of the Committee on Cooperation with Nonmedical Groups and Societies is reported in full, except for the portion with respect to child adoption. This is being returned to the committee with the request that it give this portion of the report its very careful attention and resubmit it to the Executive Board. The report was accepted as read. Before accepting this report, the Executive Board had an extensive conference with Dr. Lee Forrest Hill, chairman of the committee, and Dr. Warren M. Cox, Jr., of Mead Johnson & Company, both of whom were present at the meeting.

The report of the Committee on Medical Supervision of Camps was accepted.

The report of the Liaison Committee for the American Academy of Pediatrics with the American Medical Association was filed.

The Committee on Hospitals and Dispensaries reported that it was making a survey of the facilities for dental care in children's hospitals. The report was accepted as read.

The report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases was accepted as read. The committee has made a careful summary of chemotherapy in childhood. This is being mimeographed, and a copy of the summary is to be sent to each member of the Academy in the near future.†

The Committee on Infantile Paralysis reported that its chairman had been made a member of the Committee on Education of the National Foundation for Infantile Paralysis. They are working upon the teaching in the various medical schools in regard to infantile paralysis. The report was accepted as read.

The Committee on Legislation reported upon the National Health Bill. The chairman of this committee had a personal conference with Senator Murray, and the point of view of the Academy as expressed at the meeting in Cincinnati in

*Since the meeting, we are told by the chairman of the committee that another scholarship has been arranged.

†This report is to be published in the July issue of the JOURNAL.

November, 1939, was presented. The chairman has also spent considerable time with Dr. Martha Eliot, chairman of the Technical Committee of the National Health Conference, going over the Wagner Bill with the idea of proposing some changes which would not be discriminatory to pediatricians. The committee regards it as extremely unlikely that "Congress will take any action on any measure affecting the interests of our members during this session except on H.R. 8240 relating to the appropriation of ten million dollars for the construction of hospitals." The report was accepted as read.

The Committee on Medical Education had nothing special to report. It called attention to the fact that there was no letup in the number of men entering pediatrics, since the American Board of Pediatrics has nearly two hundred candidates up for examination for certification in 1940.

The Committee on Mental Health, aside from its urging a development of a motion picture which has been mentioned previously, also suggested a plan for emphasizing the need for teaching mental health in the pediatric departments of medical schools. Articles on mental health, sponsored by the committee, are appearing in the JOURNAL OF PEDIATRICS. The report was accepted as read.

The Committee on Nursing Education has nothing further to report.

The Committee on Problems of the Fetus and the Newborn Infant reported that it has joined with a joint committee from pediatric and obstetric societies. This joint committee will work along this line, and reports of the progress of this work will be presented to the Academy from time to time. A resolution to this effect was presented by Dr. Stanley Nichols as coming from Region I; it was referred to this committee for consideration.

The report of the Committee on School Health and School Health Education was not acted upon at the meeting of the Executive Board. It was a lengthy report, and the Board members felt that it would take some time to digest it. It, therefore, will not be acted upon until the meeting of the Academy in November, by which time the Executive Board will have had ample time to review this report thoroughly.

The Committee on Therapeutics and General Therapeutic Procedures, although it had no concrete report to offer, mentioned tentative plans for representation in the revisions in the United States Pharmacopoeia and National Formulary; a plan for reducing further the incidence of lead poisoning and fatality in infants and children; and suggestions for education of parents as to the dangers of certain potent remedial agents that might be left around the household carelessly.

The Committee on Vitamins reported progress in the preparation of the pamphlet which is to be sent to the members later.

The situation of the Council for Pediatric Research was discussed at length. It was decided to support this for another year to an amount not to exceed $500. The Council was to be made, under these conditions, a committee of the Academy and not an autonomous unit. It was asked to define more definitely its policies.*

Dr. Otto L. Goehle reported progress in his work in making an estimate of the geographic distribution of pediatric practice.

The length of appointment for state chairmen was discussed. This was considered to be largely a regional affair, and it was decided to continue the custom of reappointment each year.

It was decided that the Executive Board would recommend the institution of an "affiliate" membership, such members to be appointed for one year and to be eligible for re-election.

*Dr. Oscar M. Schloss was reappointed to the Council for Pediatric Research for five years.

The request of Dr. Alexander T. Martin of New York, N. Y., that the Academy assume supervision of The Mother's Milk Bureaus in the United States and Canada was rejected because it was felt that the Academy had so many activities at present that it could not assume more.

The secretary was empowered to spend up to $25 for the Henry Dietrich Memorial.

On request of Dr. Hugh Leslie Moore, associate chairman of Region II, it was decided that the inclusion of Missouri and Maryland in Region II should depend upon a poll of the members from these two states.

The request of Dr. Charles W. Martin, Far Rockaway, N. Y., for a duplicate certificate was not granted.

The secretary was empowered to investigate having certificates mounted on plaques and to report on it at next meeting.

The offer of the *Science News Letter* at a reduced rate for members of the Society, at the request of individual members, was accepted.

The meeting adjourned at 12:30 A.M., Monday, May 6, 1940.

Report of the Committee on Cooperation With Nonmedical Groups and Societies

Your committee wishes to report satisfactory progress in its major activity, namely, cooperation with the National Parent-Teachers Congress in an attempt to further the objectives of the Summer Round-Up of the Children movement. Briefly, the committee's program in this connection can be outlined most readily in the following numerical paragraphs.

1. Establishment of local state subcommittees in each state in the country whose visualized functions will be (1) to act as an advisory or consultatory source to the local P.-T.A. officials, (2) to stimulate interest in their respective states in improving the quality and quantity of health examinations of children through arrangement of place on the program before state, county, or other medical meetings, through publication of articles in local medical journals, and through demonstration of well-conducted examinations in as many centers as possible in each state during the period of the Summer Round-Up campaign, and finally (3) to inform and enlist the active support for the Academy's program of all Academy members and as many of the other physicians of the state as possible whose work embraces children.

2. Production of a sound motion picture film outlining the essential procedures in a reasonably adequate health appraisal of a normal child of school age.

3. Preparation of a brochure supplementing the film, but in itself embracing minimum standards.

To make clear the present status of the committee's program, each of these paragraphs needs amplification. Concerning the state subcommittees, it may be said that appointments have been made in all the states and that most of the committees have been in operation for approximately a year. In response to a questionnaire to all state subcommittee chairmen last fall, twenty-nine replies were received. In only nine of the states had a conference with local P.-T.A. officials been held. Nine additional states indicated that conferences were planned for the future. During the Cincinnati meeting the national committee met with representatives of the state subcommittees at a luncheon meeting. Twenty-five of the forty-eight states were represented. The whole cooperative project was thoroughly explained and discussed, including the point of view of the P.-T.A., which was presented by Dr. Lillian Smith, chairman of the National Summer Round-Up of the Children. The members of the national committee were gratified at the interest evidenced by the state committee members in the program, and they believe that the opportunity thus afforded to discuss its features directly will do much to stimulate activity in the various states.

Undoubtedly, the most important, and what has every promise of being the most valuable, part of the program is the sound motion picture film. The picture has been completed and had its first showing before the Region I meeting at Washington on April 4. Several comments should be made about this film. In the first place, both the committee and the Academy owe a debt of thanks to Dr. Arthur H. Parmelee for the many hours of work he spent in assisting with the preparation of the scenario and in acting as technical advisor during the filming process, and to Mead Johnson and Company for making it financially possible for the Academy to have the film. The filming was done by a professional concern, and professional actors and actresses were employed. Obviously, the expense incurred was considerable.

The picture is listed under the title of "When Bobby Goes to School." It is a 16 mm. film and requires twenty-five minutes for showing. It is, of course, necessary to have a sound projection apparatus and to have an empty 800-foot reel upon which to wind the film, which is continuous.

Certain rules governing distribution of the film have had to be set up for obvious reasons. These rules have already been submitted to and adopted by the Executive Board, but in the interests of completeness of this report, they are listed here.

1. That the committee incorporate as part of their report, to be sent to all members of the Academy, the complete scenario as presented in the first draft at its Cincinnati meeting. (Accomplished.)

2. That the chairman of the Committee on Cooperation with Nonmedical Groups and Societies take the responsibility for arranging showings before all regional meetings of the Academy during the next year.

3. That the Committee urge all members of the Academy to take the initiative in arranging for a showing of the film before their local medical groups.

4. That to facilitate these various actions, Mead Johnson & Company will be pleased to have its various representatives help in arranging details of projection, provided the showing is to medical groups.

5. That the committee recognizes that this education film will accomplish its major purpose only if seen by the maximum number of people, and requests Mead Johnson and Company, because of their experience in the ethical distribution of motion picture films, to take full charge of distribution.

6. It is understood that film will be released only on the request or sponsorship of a physician. When anyone proposes to use the film, he will be required to secure the written permission of a responsible official of the county medical society in the county in which he proposes to show the film.

7. Mead Johnson and Company is requested not to sell copies of the film to any individual, group, or organization.

Already commitments have been made to show the film before the Region III and IV meetings of the Academy, before the Pediatric Section meeting of the American Medical Association in June, and before several state medical meetings. The state subcommittees will be urged to make arrangements for having the picture placed on the program of all state medical meetings and those of as many county and other medical meetings as possible during the coming year.

The committee hopes that certain results will come from widespread showing of this film to physicians. Primarily, it is hoped that a clear conception may become established as to what constitutes a reasonable health appraisal of a preschool and school-age child. It is hoped that the procedure depicted in the film will gradually come to be accepted as a standard that ought to be employed whenever a child is presented to a physician for a health examination. While the original purpose of the film was in connection with the Summer Round-Up of the Children as a means of demonstrating the scope of the examination desired, it is

now apparent that its educational possibilities extend even beyond this activity, important as it is, and it should serve as a stimulus and an example to the physician not only to make better health examinations, but to make better examinations on all children whom he is called upon to treat. Finally, it may be said concerning the film that it represents the combined consensus of the American Academy of Pediatrics and carries with it the authority and prestige of that body; every member reviewed the scenario, and submitted criticisms, in so far as possible, were incoroporated in the final draft.

The third portion of the Committee's program is now in process of preparation. This is a brochure intended to amplify those points which could only be suggested in the film. Its purpose will be to present briefly and concisely up-to-date information which the general practitioner and pediatrician need to know in carrying out the details of a reasonably thorough health appraisal of a child. It is intended to discuss not only the important features of the physical examination, but also other equally important phases of child health such as behavior, emotional stability, social adjustment, and nutritional needs. Stressed will be the point that a well-executed health examination provides an unexcelled opportunity for parental education which is largely missed in hurried group examinations. These are the aims embodied in the health program of the National Parent-Teachers Congress, designed to be carried out through the Summer Round-Up of the Children. In the cooperative program thus outlined your committee hopes the groundwork may be laid for some progress along the slow road of education in broadening the field of preventive pediatrics.

Finally, your committee wishes to present the report of Dr. Albert D. Kaiser which was submitted to the committee at its meeting in Cincinnati, November 16. This report pertained to the present status of medical supervision of nursery schools. This subject had previously been suggested to the committee as a possible field for Academy cooperation.

Dr. Kaiser's report reads: "The rapid development of the nursery schools in many communities has created a new focus for the grouping of young children. The health problem for nursery schools is not unlike that of larger and well-established schools. Inasmuch as they are frequently inaugurated under private auspices, there was some uncertainty as to the health provisions instituted in connection with the schools.

"I communicated with a number of authorities in New York State and in Washington. These directors all agreed that health supervision of nursery schools is not only desirable, but essential. In the correspondence and from conversation with nursery school authorities, I learned that excellent medical supervision is now provided for nursery schools affiliated with institutions or supported by foundations. The medical supervision of privately conducted schools is variable, excellent in some instances and absolutely lacking in others.

"In some communities the local health authorities must approve the establishment of a nursery school, and the policy of health supervision is directed. This applies to privately as well as publicly conducted schools. Supervision by the local health authorities, either city or county, would be the most satisfactory method of correcting this neglect in such schools in which no provision is made for health direction of the pupils.

"I believe this committee could transmit to the state chairmen the suggestion that the health supervision of nursery schools is inadequate in many instances. Although excellent provision is assured in some nursery schools, there is no assurance that a responsibility exists for such protection. Through their local committees state chairmen could bring the importance of this matter to the attention of the local health officers who are in best position at present to see that every school has a minimum standard for health provision.

"This procedure has the approval of a number of authorities interested in nursery schools."

Your committee recommends:

1. That the part of this report dealing with the sound motion picture film be published in the JOURNAL OF PEDIATRICS as soon as possible in order that the Academy members may be informed of its availability, its purposes, and its rules for distribution.

2. That the report of Dr. Kaiser also be published in order that the Committee may learn of any Academy interest in the subject.

Respectfully submitted,

Committee on Cooperation With Nonmedical Groups and Societies

Lee Forrest Hill, Chairman
Dennis H. Kelly, Secretary
C. A. Aldrich
James W. Bruce
Joseph H. Johnston
Albert D. Kaiser
Margaret M. Nicholson
Warren R. Sisson
Henry E. Utter

Report of the Committee on the Medical Supervision of Summer Camps

I. Precamp Examination. Purpose: To select children able to participate in the usual summer camp activities and to detect acute infectious diseases.

A. Examiner to be a physician familiar with medical problems of children.

B. Time of examination to be preferably two weeks before entrance to camp and not longer than one month.

C. Form for physical examination to be similar to that recommended by the Camp Committee of the American Academy of Pediatrics and to include recommendations of examining physician.

D. Compensation to physician to be paid by parent or camp organization. Standard fee to be established by local groups.

II. Medical Supervision at Camp.

A. Medical personnel to consist of physician and nurse; also dietitian in large camp units. The camp physician should be in residence or in the capacity of visiting physician. The nurse should always be in residence. The dietitian should be in residence or in visiting capacity.

B. Qualifications of personnel.

1. The camp physician should have had at least five years' experience in medical practice. He should be familiar with the usual medical problems of children. He should be in residence if possible. A camp physician should be available at all times.

2. The camp nurse should be a graduate of an approved school of nursing, with at least three years' experience of graduate nursing, and should be familiar with the nursing problems of children.

3. The camp dietitian should have had training in a recognized school of dietetics and should have had at least one year's practical experience. The duties of a dietitian may be filled by a qualified nurse with adequate dietetic training.

C. Duties of personnel.

1. Duties of camp physician.
   a. Sanitary inspection, either independently or in collaboration with state health department, should consist of examination of food handlers, with special reference to typhoid, tuberculosis, and syphilis; and investigation of water supply, sewage disposal, and milk supply.
   b. Physical examination of children to be made within forty-eight hours after admission to camp. Standard forms for examination to be used.
   c. To give health talks and first-aid instruction.
   d. To render medical and surgical care to campers and staff.
   e. To report all illneses, injuries, and physical defects to parents.
   f. To supervise the nursing care of campers and staff.
   g. To provide and make available facilities of a well-equipped infirmary, with provision for isolation.
   h. To select and make available facilities for Class A hospital.
   i. To supervise camp routine with reference to rest, food, and exercise.
2. Duties of camp nurse.
   a. To render first aid to staff and campers in absence of camp physician.
   b. To render nursing care to all sick campers and staff.
   c. To report daily all illnesses and injuries to camp physician.
   d. To assist camp physician in physical examinations.
   e. To supervise camp diets in absence of dietitian.

ANNUAL MEETING, REGION II OF THE AMERICAN ACADEMY OF PEDIATRICS

The annual meeting of Region II of the American Academy of Pediatrics was held on March 15 and 16, 1940, at the Edgewater Gulf Hotel, Edgewater Park, Miss. The program consisted of two panel discussions on "The Hematology and Anemias of Infancy and Childhood" and "Pediatric Surgery." There were two round table discussions on "Intracranial Injury in the Newborn" and "Sulfanilamide and Sulfapyridine." A general program of pediatric interest was given on the afternoon of March 15. Guest speakers at the evening meeting were Dr. Felix J. Underwood, executive officer of the Mississippi State Board of Health, who talked on "The Opportunity for Preventive Medicine in Pediatrics," Dr. William Harvey Perkins, Professor of Preventive Medicine at the School of Medicine of Tulane University of Louisiana and president of the Tuberculosis and Public Health Association of Louisiana, who talked on "Changing Concepts of a Typical Case of Tuberculosis Infection."

Business Meeting of Region II, March 16, 1940

In the absence of Dr. Edward C. Mitchell of Memphis, regional chairman, Dr. Hugh Leslie Moore of Dallas, associate regional chairman, called the meeting to order. Those states represented were Arkansas, Alabama, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Texas, and Virginia. Florida, Kentucky, Oklahoma, and West Virginia were not represented.

Sixty Fellows of the Academy in Region II were present. Dr. Joseph B. Bilderback, Portland, Ore., president of the Academy, Dr. Clifford G. Grulee, Evanston, Ill., secretary of the Academy, Dr. Jessie M. Bierman, Children's Bureau, Washington, D. C., and Dr. Hugh L. Dwyer, Kansas City, Mo., were present. One hundred and one guests were registered.

The chairman asked if any state problems or any unfinished business was to be brought up for discussion.

Dr. Gilbert Levy of Memphis stated that Dr. Arthur G. Jacobs, Memphis, was working out some means whereby there might be a weaving of activities between the pediatric group within the state and the Children's Bureau.

The chairman then called for new business.

Dr. Warren Quillian, Coral Gables, Fla., and Dr. James B. Stone, Richmond, Va., were nominated as associate regional chairmen.

Dr. Hugh Leslie Moore of Dallas, incumbent associate regional chairman, was nominated regional chairman.

The chairman then brought up for consideration the time and place of the next meeting.

The chairman announced that Richmond, Va., had invited Region II to hold its next meeting in that city. There were no other invitations. It was voted to meet in Richmond.

Dr. Grulee told the group what was happening in other regions. He explained that Regions III and IV have committees who attend to programs, exhibits, and finances. They establish regional finances, with a background of some hundreds of dollars, and the whole thing can then be worked out systematically. In this manner, it is possible to develop in a region the kind of program it wants, as well as a

clientele, and the meeting can be financed very easily. He announced that this plan is being worked out in Region I also. It was his belief that, in view of the fact that this is the first independent meeting that Region II has had, it might be well now for the region to take this matter into consideration and formulate some plan in this direction. A committee was appointed to work this plan out.

Dr. Gilbert Levy proposed that, in view of the fact that it was the general consensus of opinion that this first independent meeting of Region II of the American Academy of Pediatrics had been a most successful one, a rising vote of thanks be tendered to the members of the committee, to Dr. Robert A. Strong, to Dr. Harvey F. Garrison, and to all those who helped to make it a success.

There was no further business and the meeting adjourned.

News and Notes

At the fifty-second annual meeting of the American Pediatric Society at Skytop Lodge, Skytop, Pa., May 2-4, 1940, the following members were elected officers for 1940-41: president, Dr. Thomas B. Cooley, Detroit; vice-president, Dr. Grover F. Powers, New Haven; secretary-treasurer, Dr. Hugh McCulloch, St. Louis; recorder-editor, Dr. Heyworth N. Sanford, Chicago; councilor, Dr. A. Ashley Weech, New York. The following were elected to membership in the Society: Dr. Stewart H. Clifford, Boston; Dr. Francis F. Schwentker, New York; Dr. Charles A. Weymuller, Brooklyn; Dr. Harriet G. Guild, Baltimore; Dr. Paul Gyorgy, Cleveland; Dr. John A. Bigler, Chicago; Dr. T. F. McNair Scott, Philadelphia; Dr. John P. Caffey, New York; and Dr. Clement A. Smith, Boston.

The Society for Pediatric Research on May 1, 1940, elected the following members as officers for the year 1940-41: president, Dr. A. Ashley Weech, New York; secretary, Dr. Mitchell I. Rubin, Philadelphia.

Dr. William J. Orr has been appointed Professor of Pediatrics and Head of the Department at the University of Buffalo Medical School. He succeeds Dr. DeWitt H. Sherman, emeritus professor who died recently.

Dr. Stanley Gibson has been appointed Professor of Pediatrics and Head of the Department at the Northwestern University Medical School, Chicago. Dr. Gibson succeeds Dr. Isaac A. Abt.

Dr. James W. Bruce has been appointed Professor of Pediatrics and Head of the Department at the University of Louisville Medical School. Dr. Bruce succeeds Dr. Phillip Barbour.

Book Reviews

Your Baby and How to Care for It. Lindsey W. Batten, M.D., M.R.C.P. New York, 1940, Harper and Brothers. Pp. 182. Price $1.50.

Let's Talk About Your Baby. H. Kent Tenney, M.D., F.A.A.P. Minneapolis, 1940, University of Minnesota Press. Pp. 115. Price $1.

Approximately a hundred books—good, bad, and indifferent—on the care of the baby have been published for lay consumption. As all cover more or less the same ground, and the differences, except in style, consist chiefly in the expression of relatively unimportant viewpoints or idiosyncrasies of the authors, they are rarely given review space in the JOURNAL. As a rule, they add little or nothing to the literature or advancement of pediatrics, and their circulation is in large part limited to the practice of some one pediatrician or locality. It was the late Dr. L. Emmet Holt, Sr., who started this never-ending procession many years ago with the little volume, *Care and Feeding of Children*, which was a household classic in the early part of this century.

By coincidence, two books in this field came to the reviewer's desk recently which are so outstanding that the usual boresome task of reading became a pleasure. While both have the same purpose and cover the same ground to a certain extent, they are as different as night from day. Each has a distinctive style and, while we do not believe Dr. Batten's book could have been written by an American, we cannot conceive of Dr. Tenney's with an English author.

Your Baby, by Dr. Batten, an English physician on the staff of the Children's Hospital in Hampstead where he is engaged in "general practice," covers not only the care and feeding of the infant, but the first two chapters, based upon his own experience, have to do with pregnancy and the child before birth. This, in the United States, would have meant a compilation of obstetrician and pediatrician. Although the advice frequently differs in details from current American practice, the author is so sane in his viewpoints, so understanding of the problems of the young prospective mother and the mother with young children, and above all writes with a style so delightful and humorous that the book is outstanding. After a discussion of nursing, artificial feeding, and diet, it concludes with three chapters on "bad habits" and "management" which alone are a noteworthy contribution. This coverage makes it rather unique, and it is one of the few books in this field that a doctor might want his own child to read. It is obvious that Dr. Batten is preaching what he practices and that his patients are very fortunate individuals. There is a brief foreword by H. G. Wells that might just as well have been omitted.

Let's Talk About Your Baby, by Dr. Tenney of the Wisconsin School of Medicine, was written in 1934 and privately published by Dr. Tenney for his patients. Reports of the book gradually circulated around, and in this way it came to the attention of a number of pediatricians who became enthusiastic about it. Now the book, with minor revisions, has been issued in an attractive format by the University of Minnesota Press and is available for general distribution. It is distinctly American in its subject matter, make-up, and style. Dr. Tenney starts each chapter in a colloquial, even slangy, sort of way, and then gradually passes over into sound straightforward advice written in a simple direct way. Dr. Tenney, like Dr. Batten, has a knack of expression that carries over the meaning to register in the lay mind.

The last chapter, "Important Events in the Early Life of Your Baby," gives a place to enter data graphically regarding the baby's development. There is an excellent short foreword by Dr. Brennemann.

The change of title of Dr. Batten's book has interested us. In England it is published under the distinctive and attractive title, *The Single-Handed Mother.* Why the change to the commonplace mediocre title, *Your Baby,* for the American public? It is paralleled curiously enough by the publication in England of the Aldrich book, *Babies Are Human Beings,* under the title of *Understand Your Baby.* At least things, so far as titles are concerned, have been evened with our English colleagues, but the minds of publishers are beyond understanding.

B. S. V.

A Manual of the Common Contagious Diseases. Philip M. Stimson, M.D. Third edition. Philadelphia, 1940, Lea and Febiger. Pp. 467. Price $4.

The third edition of Stimson's manual has been thoroughly revised and rewritten to an extent that practically makes it a new book. Controversial questions are handled with impartiality. The newer chemotherapeutic methods of treatment are included. Five excellent color plates have been added. The new edition will undoubtedly hold for this manual the position which it has so justly obtained.

The Compleat Pediatrician. W. C. Davison, M.D. Third edition. Durham, N. C., 1940, Duke University Press. Price $3.75.

There is no such radical change in the third edition as was made in the second edition of this book published two years ago. Many minor changes have been made which bring the material to date and are in keeping with the rapid progress of pediatrics in the last two years. The book continues to remain "a veritable mine of information" and is invaluable for the office desk.

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